PART I

THE CONFIGURATIONAL STABILITY OF PRIMARY GRIGNARD REAGENTS

PART II

APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY TO THE STUDY OF MOLECULAR ASYMMETRY

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ABSTRACT

PART I

THE CONFIGURATIONAL STABILITY OF PRIMARY GRIGNARD REAGENTS

Examination of the temperature dependence of the nuclear magnetic resonance spectrum of 3,3-dimethylbutylmagnesium chloride in diethyl ether solution indicates that inversion of configuration at the methylene group of this Grignard reagent occurs with an approximate rate of 10 $sec.^{-1}$ at room temperature. The dependence of the rate of inversion on solvent and on the structure of the Grignard reagent is discussed in terms of possible mechanisms for the inversion.

PART II

APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY TO THE STUDY OF MOLECULAR ASYMMETRY

The methylene protons of 1-phenylethyl benzyl ether are magnetically non-equivalent and display an AB-type nuclear magnetic resonance spectrum. The variation in the spectrum of this compound and in the spectra of other structurally similar ethers with solvent indicates that the principal contribution to the magnetic non-equivalence of the methylene protons originates in the magnetic anisotropy of the phenyl group bonded directly to the methylene group. It is suggested that the solvent dependence of these spectra reflects changes in the populations of the possible rotational conformations open to the molecule.

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INTRODUCTION

The configurational stability of Grignard reagents has long been a subject of investigation in organic chemistry. Activity in this area has been a consequence not only of interest in the classical problems of the structure of the Grignard reagent and the stereochemistry of its reactions, but also of a more recent concern with details of the nature of carbon-metal bonds.

The best explored approach to this problem has been comparison of the stereochemistry of products obtained from carbonation or oxidation of a Grignard reagent with that of the halide from which it was obtained. In those compounds in which the carbon bonding orbital directed toward the metal has hybridization close to sp^2, it now seems probable that inversion of configuration is slow (1). Thus, both cis- and trans- isomers of 2-bromobutene-2 have been converted to the corresponding acids with complete retention of configuration via the Grignard reagents (2), and the Grignard reagent from (+) 1-bromo-1-methyl-2,2-diphenylcyclopropane has been shown to possess a high degree of configurational stability (3). These observations are in agreement with the configurational stability of the more carefully studied alkenyllithium (4,4) and cyclopropyllithium (3,5) compounds.

Attempts to measure the configurational stability of organomagnesium compounds in which the carbon bonding orbital directed toward the metal is sp^3 hybridized have been less fruitful (6). With the one exception of a configurationally stable dialkylmagnesium compound (7), every reliable examination of the optical purity of products obtained from optically active halide by means of the corre-

sponding Grignard reagent has led to the conclusion that complete racemization had occurred at some point during the reaction sequence.

Unfortunately, this observation of racemization in products several reactions removed from starting material does not allow a decision to be made concerning the optical stability of the organometallic compound itself. Racemization might have occurred during formation or reaction of the Grignard reagent, as well as during its lifetime. Although little evidence is available concerning the importance of racemization during reaction, several data suggest that extensive racemization may occur during preparation of the Grignard reagent under the usual conditions from magnesium metal and halide.

The most direct of these is Walborsky's observation that the acid obtained on carbonation of 1-methyl-2,2-diphenylcyclopropyl Grignard reagent displayed a complete retention of optical activity only if prepared from its lithium analog by reaction with magnesium bromide or methylmagnesium bromide (3). The organolithium compound, in turn, had been prepared by metal-halogen exchange between the cyclopropyl bromide and n-butyllithium. If the Grignard reagent was prepared by direct reaction between halide and magnesium turnings, then only 10-15% optical purity was observed in the products.

Walborsky concluded from these experiments that racemization on the metal surface occurred to an important extent during formation of the Grignard reagent. Subsequently, other workers have reported data suggesting that the intermediate formed initially in reaction between an alkyl halide and magnesium metal may resemble an alkyl radical. Rüchardt (8) in particular has isolated products from the

reaction of neophyl chloride with magnesium which are characteristic of the radical neophyl rearrangement (9), and Hamilton has rationalized certain of the products from reaction of cyclobutyl chloride and cyclopropylcarbinyl chloride with magnesium on the basis of radical surface reactions (10).

It is interesting to note in this connection that the surprising difference between the apparent configurational stabilities of organolithium and organomagnesium compounds may be an artifact of their preparation. Thus, although lithium is more electropositive than magnesium by 0.2 units on the Pauling electronegativity scale (11), and might therefore be expected to form the more ionic bond with carbon, two lithium alkyls, sec-octyllithium (12) and sec-butyllithium (4), have been prepared and shown to be moderately configurationally stable; all attempts to prepare configurationally stable alkyl Grignard reagents have been unsuccessful (6). Grignard reagents, however, are commonly prepared by reaction between alkyl halide and magnesium, and lithium alkyls are prepared by metal-halogen or metal-metal exchange reactions. Reutov's recent preparation of optically active dialkylmagnesium compounds is compatible with this suggestion, because a mercury-magnesium exchange reaction, using optically active alkylmercurial, was used for their preparation.

Despite ambiguities associated with interpretation of the numerous experiments directed toward determination of the configurational stability of Grignard reagents, qualitatively it seems clear that not all of the racemization observed in products derived from these organometallics occurs during their formation or subsequent

reaction. However, relatively little thought has been devoted to possible mechanisms for this racemization, primarily because so little is known concerning the detailed structure of Grignard reagents (14). A detailed review of this latter subject is beyond the scope of this thesis; however, several recent experiments are pertinent to this discussion.

Most modern work concerned with the structure of Grignard reagents has centered around attempts to evaluate the success of the so-called Schlenk equilibrium (14,15) in describing the Grignard reagent. Dessy and co-workers have studied the exchange reaction

$$2RMgX \rightleftharpoons R_2Mg \cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2.$$

between labeled magnesium bromide and diethyl- (16) and diphenylmagnesium (17). Only limited exchange between magnesium bonded to carbon and magnesium bonded to halide was observed when ^{28}Mg was used as the tracer; however, complete exchange occurred when ^{25}Mg was used (17). Dessy decided that the complete exchange result was spurious and due to impurities in the ^{25}Mg sample used. The ^{28}Mg experiment lead him to conclude that the equilibrium

$$2RMgBr \rightleftharpoons R_2Mg + MgBr_2$$

was not important in the Grignard reagents studied (18). In addition, conductiometric measurements were reported to give identical (21) values for the dielectric constant of 1:1 mixture of diethylmagnesium and magnesium bromide and of an equivalent concentration of "ethylmagnesium bromide" (22). It was therefore concluded that the Grignard reagents studied were best represented by the equilibrium

$$R_2Mg \cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2$$

and that no species represented by the formula "RMgX" is present in solution.

Recently however Stucky and Rundle (23) and Ashby and Becker (24) have presented data suggesting that Dessy's conclusion may have been premature. Stucky and Rundle demonstrated by the X-ray crystal structure determination of phenylmagnesium bromide dietherate that the magnesium atom was tetrahedrally coördinated to one phenyl group, one bromide atom and two oxygen atoms.

Ashby and Becker were able to obtain a crystalline solid from a tetrahydrofuran solution of ethylmagnesium chloride whose empirical formula corresponds to $EtMg_2Cl_3 \cdot THF$. This fact, and their observation that ethyl Grignard reagent was monomeric in tetrahydrofuran, led them to conclude that the most important species in solution was actually EtMgCl.

Both of these studies depended on compounds existing in the solid state, and neither is necessarily pertinent to the structure of the Grignard reagent in solution. However, the X-ray study in particular provides evidence that "RMgX" may exist under suitable conditions, and suggests that further work on the structure of Grignard reagents in solution must take into consideration the possibility of its existence.

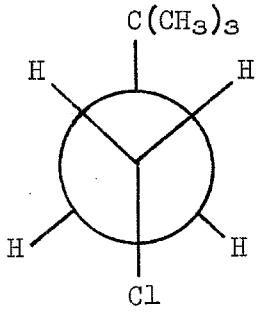
The work reported in this thesis was initiated in the hope that direct non-destructive examination of Grignard reagents in

solution by nuclear magnetic resonance spectroscopy might help to climinate some of the ambiguities associated with interpretation of the indirect destructive studies.

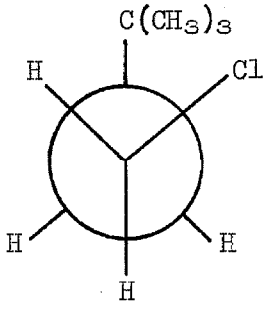
RESULTS

The n.m.r. spectrum of the methylene protons of 3,3-dimethylbutyl chloride in carbon tetrachloride or carbon disulfide solution is a typical AA'XX' spectrum (25); of 24 theoretical transitions, 20 have sufficient intensity to be observable. By contrast, the spectra of the $-CH_2X$ protons of 3-methylbutyl chloride, 3-methylbutyl bromide, 3-methylbutyl iodide, n-butyl chloride, n-butyl iodide and propyl chloride are all triplets to a first approximation.

The difference in the spectra of 3,3-dimethylbutyl chloride and these other halides is reasonably explained on the basis of the relative sizes of the substituents on the ethylene fragment. In 3,3-dimethylbutyl chloride, steric interaction between the bulky t-butyl group and the chlorine atom is such that the conformation I having these two groups trans across the ethylene moiety is of appreciably lower energy than the corresponding gauche rotamers II and III.



I



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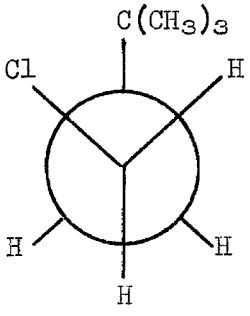


III

If rotamer I is more populated in solution than II or III, the two CH_2-Cl protons will be magnetically non-equivalent although chemically indistinguishable, because each will have a different coupling constant to one of the $(CH_3)_3CCH_2$- protons.

The observation of an AA'XX' spectrum is not compatible with an energetically favored gauche conformation, because a mixture of II and III would have only an averaged vicinal coupling constant if their interconversion were rapid, and would be expected to have an appreciable chemical shift between geminal hydrogens of the methylene groups if interconversion were slow.

The size of the alkyl groups attached to the ethylene group in the other halides is much smaller (26) than the t-butyl group of 3,3-dimethylbutyl chloride. Apparently the difference in energy between trans and gauche rotamers for the alkyl halides not containing the t-butyl group is not large enough to produce significantly different vicinal coupling constants.

The n.m.r. spectrum of 3,3-dimethylbutyl Grignard reagent is much simpler than that of 3,3-dimethylbutyl chloride: the $-CH_2-Mg$ resonance of this organometallic in diethyl ether solution at room temperature is a clean triplet, with J = 9.1 cps. The chemical shift between the two methylene groups is approximately 123 cps. (the resonance of the β-methylene group is partially hidden by the ether methyl peaks); the chemical shift of the $-CH_2-Mg$ protons is 39 cps. upfield from tetramethylsilane.

Addition of a stochiometric excess of dry dioxane to an ether solution of this Grignard reagent removes most of the magnesium chloride as the insoluble magnesium chloride dioxanate (14,29), leaving bis-(3,3-dimethylbutyl)-magnesium in solution. The amount of magnesium halide left in solution was not measured; however, Cope has reported that more than 99.6% of the halide ion present in ether

solutions of phenylmagnesium bromide and methylmagnesium chloride is removed by dioxane precipitation (29).

The n.m.r. spectrum of bis-(3,3-dimethylbutyl)-magnesium in diethyl ether at +33° is an AA'XX' spectrum (Fig. 1). Chemical shift and coupling constant data obtained by analysis of the spectrum of this compound and of the spectra of the corresponding Grignard reagent and chloride are compared in Table 1; details of these analyses are given in the experimental part.

Table I

Chemical Shifts and Coupling Constants for the Ethylene Protons of 3,3-Dimethylbutyl Derivatives at 60.0 Mcps. Protons 1 and 2 are α to the Magnesium

	I (X = Cl)[a]	II (X = MgCl)[b]	III (X = MgR)[c]
$\nu_1-\nu_3$[d]	103.1_9	123	128
J_{12}[f]	∓ 13.9	——[e]	$\mp 15.9_8$
$J_{13}=J_{24}$[f]	$\pm 5.4_5$	9.1	$\pm 4.1_6$
$J_{14}=J_{23}$	± 11.2	9.1	$\pm 14.0_1$
J_{34}	∓ 10.7	——[e]	$\mp 14.8_0$

(a) 10 ± 1% in carbon disulfide.

(b) 10 ± 2% in diethyl ether, concentration estimated by comparing the area of the $-CH_2-Mg$ resonance with that of the upfield ^{13}C methyl resonance of ether.

(c) 5 ± 1% in diethyl ether containing approximately 5% dioxane. Concentration estimated as in (b).

(d) $\nu_1=\nu_2$; $\nu_3=\nu_4$ by symmetry.

(e) Geminal coupling constants cannot be obtained from an A_2X_2 spectrum of this type.

(f) J_{12} and J_{34} are the two geminal coupling constants.

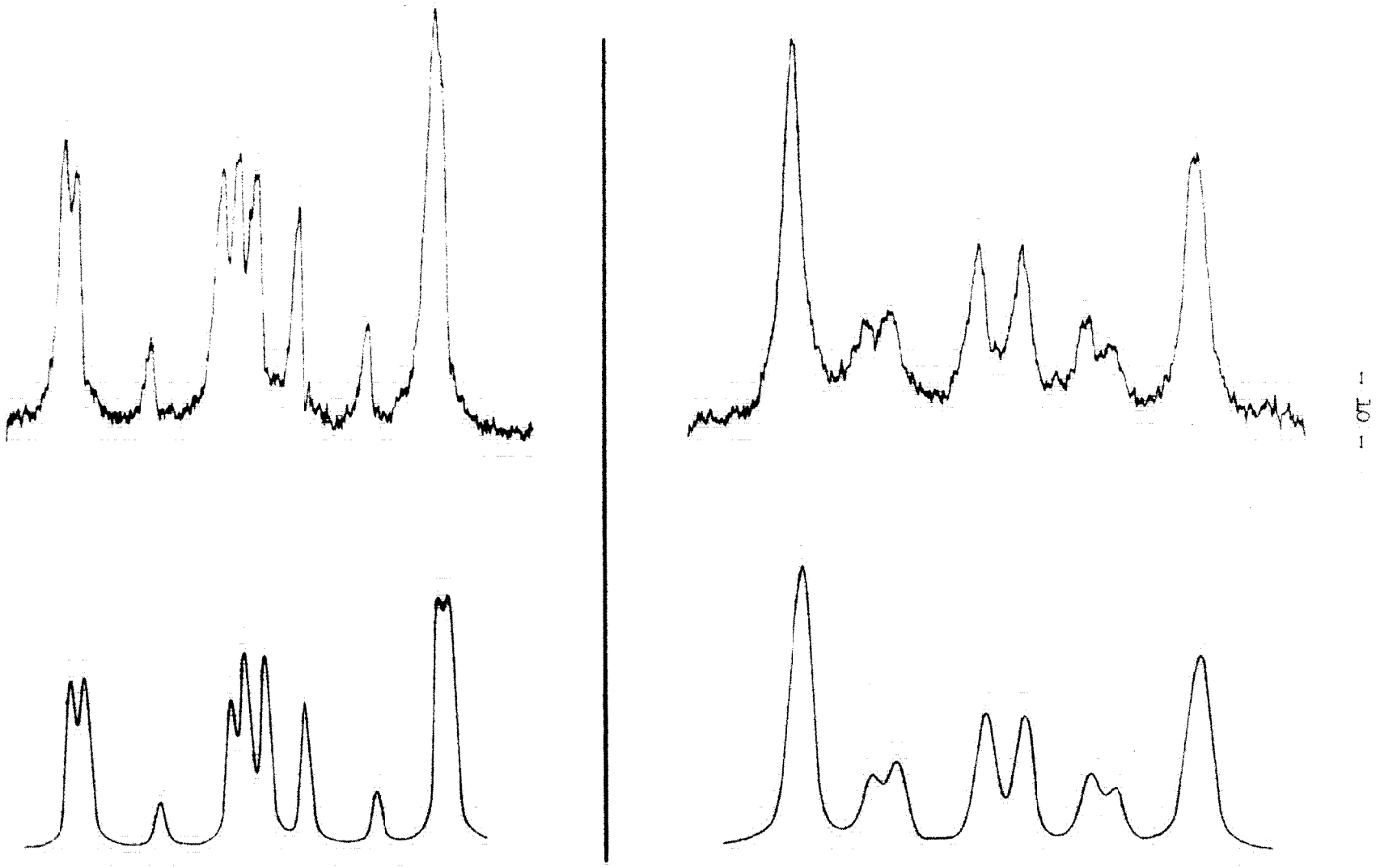


Fig. 1. Observed (upper) and calculated (lower) spectra for 3,3-dimethylbutyl chloride (left) and bis-(3,3-dimethylbutyl)-magnesium (right).

These data permit the immediate conclusion that inversion of configuration at the -CH_2-Mg center of III is slow on the n.m.r. time scale, because fast inversion would result in an averaging of the vicinal coupling constants. In addition, the magnitudes of the coupling constants make possible certain qualitative comparisons between the rotamer populations of 3,3-dimethylbutyl chloride and bis-(3,3-dimethylbutyl)-magnesium.

Karplus has calculated the dependence of J_{HH} in an ethanic fragment HCCH with tetrahedral bond angles upon the dihedral angle ϕ to be of the form of Equation 1 (30);

$$J_{HH} = A \cos^2\phi + B \qquad (1)$$

Conroy has suggested a similar relation (31). The constants A and B were originally assigned values of +9 cps. and -0.3 cps. respectively. However, the values predicted on the basis of these constants are recognized to be smaller than those observed, and Gutowsky, Belford and McMahon have been able to reconcile coupling constants observed in three halogen-substituted ethanes with Equation 1 using values of A and B of +17 cps. and -3 cps. respectively (32).

Despite uncertainties associated with A and B, and further uncertainties connected with the effects of substituents on the vicinal coupling constant (33), it seems clear that the value of 14.2 cps. observed for the larger vicinal coupling constant of bis-(3,3-dimethylbutyl)-magnesium suggests an average HCCH dihedral angle near 180°. The magnitude of this angle suggests that the molecule exists predominantly in the conformation with t-butyl group and magnesium atom trans across the ethylene fragment; extensive or exclusive

population of the gauche forms would have resulted in a smaller value of $J_{13} - J_{14}$. Correspondingly, the smaller difference in the values of the vicinal coupling constants of 3,3-dimethylbutyl chloride implies that the three possible rotational conformations in this molecule have more nearly equal energy.

These data suggest immediately that -MgR is a larger group than -Cl. Although it is not possible to give a precise measure of this difference in size on the basis of available information, a slightly more quantitative description will be possible after the temperature variation of the spectra of these organometallics has been described.

The range of a variable-temperature examination of an ether solution of a Grignard reagent is limited by two considerations: at temperatures below -50° the solutions become too viscous to give interpretable spectra; at temperatures above +120°, the possibility of explosion of the sample tube in the probe becomes important. This limited temperature range was fortunately large enough to yield several data important to the interpretation of the room-temperature spectra of these organometallics. In particular, the A_2X_2 spectrum observed for 3,3-dimethylbutylmagnesium chloride changes to an AA'XX' spectrum between +20° and -60°; correspondingly, the AA'XX' spectrum of bis-(3,3-dimethylbutyl)-magnesium collapses to an A_2X_2 type spectrum at +110°.

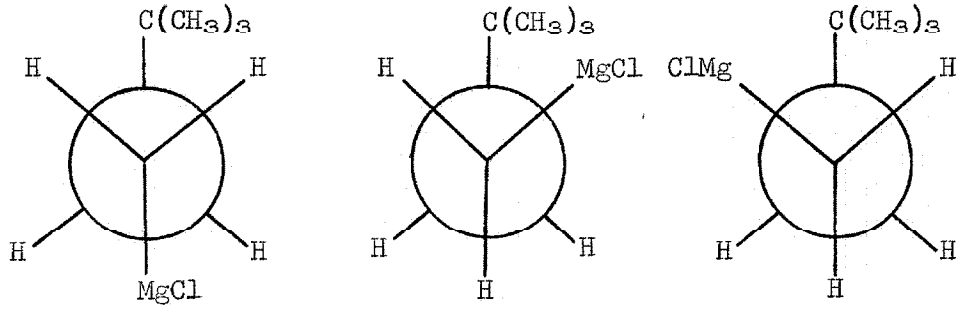
The similarity of the spectral behavior of this Grignard reagent and its corresponding dialkylmagnesium compound demonstrates clearly that a temperature-dependent equilibrium between "RMgCl" and "R_2Mg" in solution (a Schlenk equilibrium) is not responsible

for the variation in the

$$2RMgX \rightleftharpoons R_2Mg \cdot MgX_2 \rightleftharpoons R_2Mg + MgX_2$$

spectra, because little or no magnesium halide was present in the dialkylmagnesium solutions.

The averaged vicinal coupling constants observed at +33° for the Grignard reagent and at +110° for the dialkylmagnesium compound might be the result of either rapid inversion of configuration at the carbon carrying the magnesium (such inversion exchanging the magnetic environments of the hydrogens at the α-carbon atom), or else a change in relative populations of the conformations I, II and III.



I II III

Ten of the twelve theoretical lines for the A part of an AA'XX' spectrum (25) can be identified in the low-temperature spectra of Fig. 2 and Fig. 3. The 1,2 and 3,4 transitions are easily identified on the basis of intensity and position as the strong outer lines in these spectra; their separation is equal to the sum of the two vicinal coupling constants $\underline{J} + \underline{J}'$ (25). On the assumption (34) that the trans and gauche coupling constants, $\underline{J}_t$ and $\underline{J}_g$ have the same respective values for each conformation

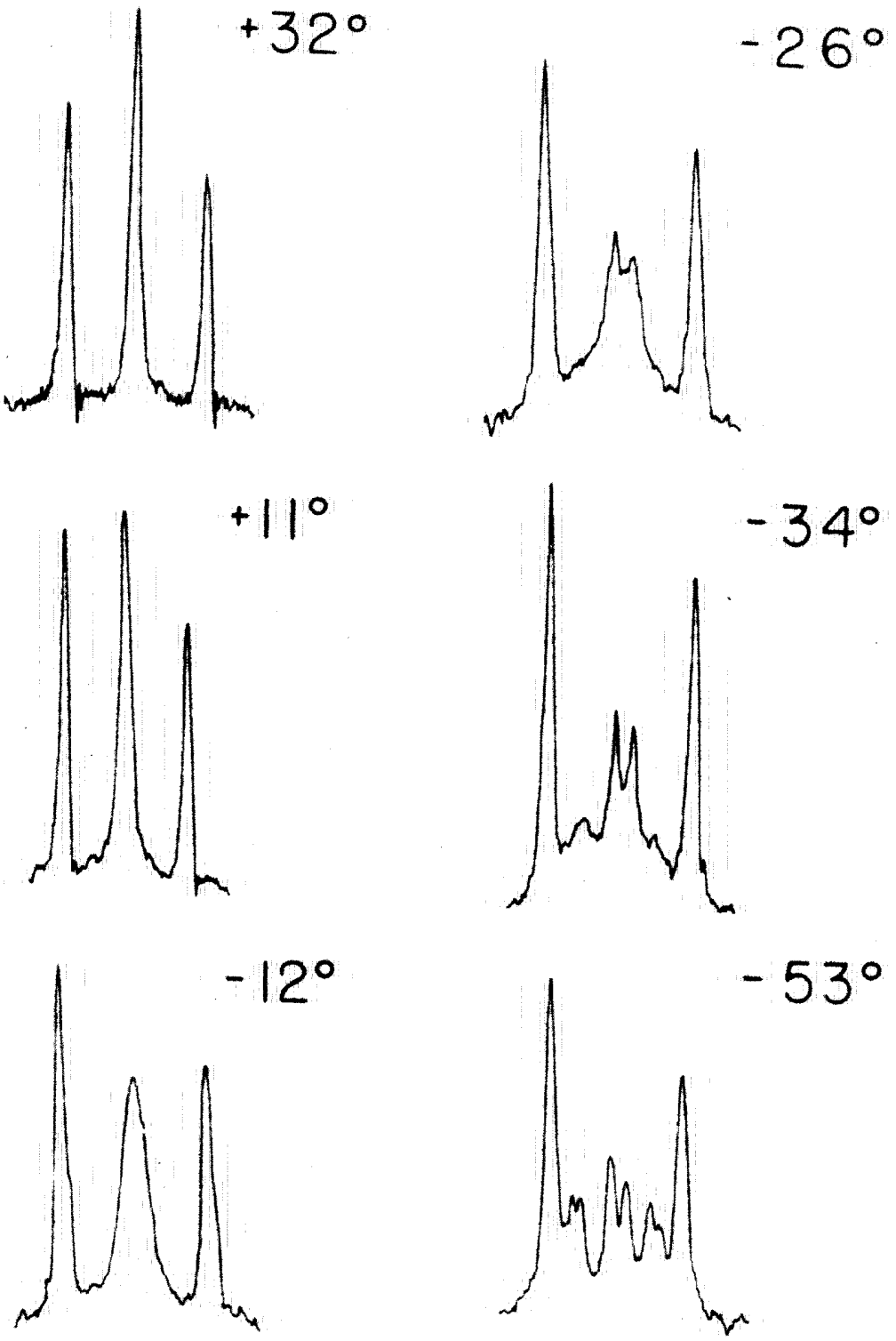


Fig. 2. N.m.r. spectra of 3,3-dimethylbutylmagnesium chloride in diethyl ether solution as a function of temperature. Only the spectra of the $\underline{CH_2}$-Mg protons are shown.

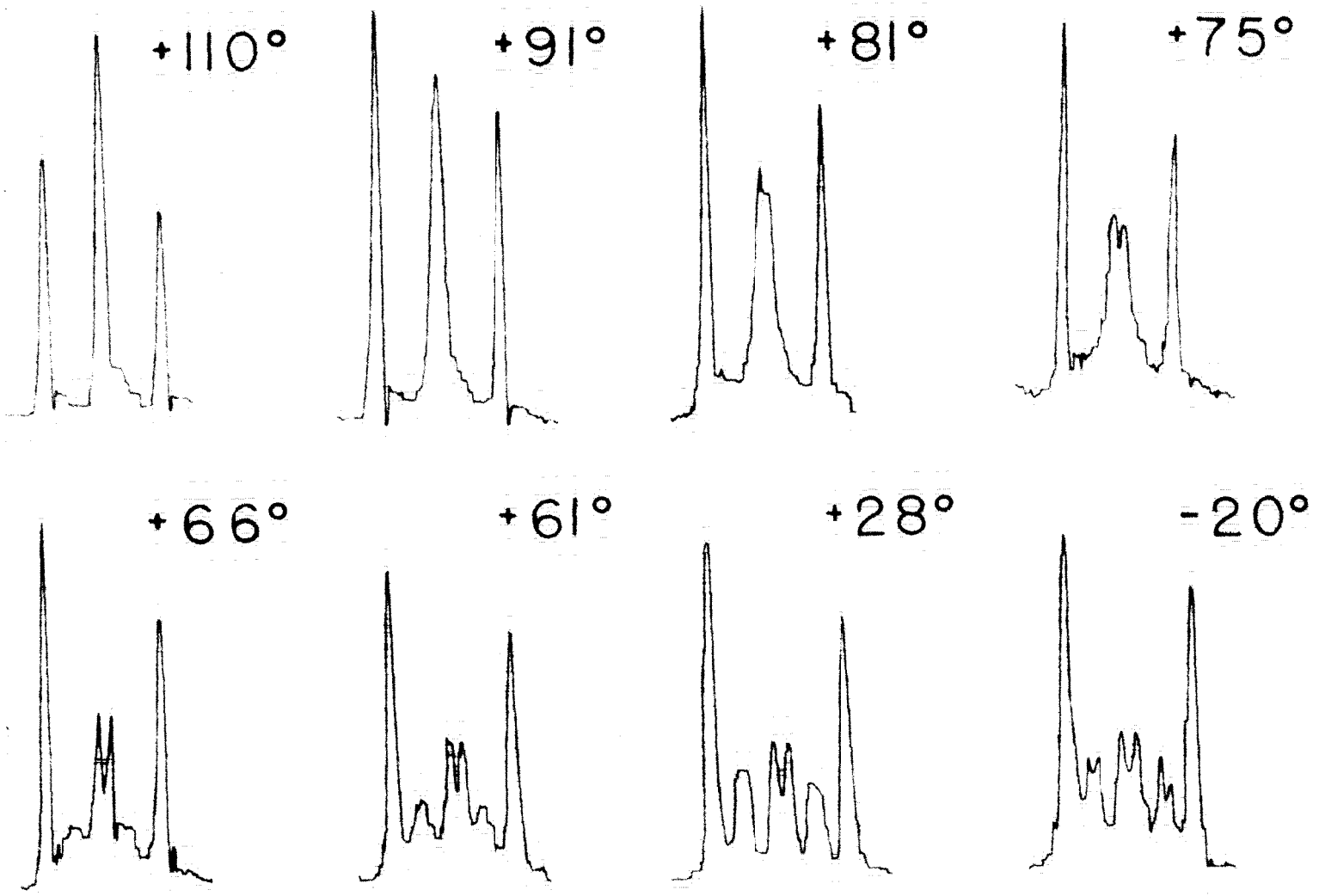


Fig. 3. N.m.r. spectra of bis-(3,3-dimethylbutyl)-magnesium in diethyl ether as a function of temperature.
Only the spectra of the $\underline{CH_2}$-Mg protons are shown.

(I-III), the separation of the outer lines for I should be $(\underline{J}_t + \underline{J}_g)$ while the corresponding separation for a rapidly interconverting mixture of II and III would be $1/2(\underline{J}_t + 3\,\underline{J}_g)$. The values reported in Table I permit a crude estimate to be made of the magnitude of $\underline{J}_t$ and $\underline{J}_g$ and consequently of the conformational populations of I, II and III.

If χ is the mole fraction of conformer I in solution, $1/2(1 - \chi)$ will be the corresponding mole fraction of conformer II and of conformer III. Assuming the trans coupling constant to be larger than the cis coupling constant,

$$\underline{J}_{14} = \chi\,\underline{J}_t + (1 - \chi)\,\underline{J}_g \qquad (2)$$

$$\underline{J}_{13} = [\chi + 1/2(1 - \chi)]\,\underline{J}_g + 1/2(1 - \chi)\,\underline{J}_t$$

$$= 1/2(1 + \chi)\,\underline{J}_g + 1/2(1 - \chi)\,\underline{J}_t. \qquad (3)$$

In order to obtain an estimate of χ, it is necessary to have values for $\underline{J}_t$ and $\underline{J}_g$; these values cannot be obtained from the experimental data in Table I alone. However, Bothner-By and Glick have shown that the magnitude of the coupling constants in substituted ethanes can be correlated with the Huggins electronegativity (35) of the substituent by the relation

$$\underline{J}^{\underline{vic}} = 8.4 - 0.4\,E \qquad (4)$$

Assuming the difference in electronegativity between chlorine and magnesium to be approximately the same on the Huggins scale as on the Pauling (11) scale ($E_{Cl} - E_{Mg} = 1.8$), the vicinal coupling constant in

CH_3CH_2X would be predicted to increase by 0.7 cps. on changing X from Cl to MgCl. The agreement between prediction and experiment

$$J_{vic}^{CH_3CH_2Cl} = 7.07 \text{ cps. (33)} \; ; \quad J_{vic}^{CH_3CH_2MgCl} = 8.6 \text{ cps.}$$

$$J_{vic}^{CH_3CH_2Br} = 7.25 \text{ cps. (33)} \; ; \quad J_{vic}^{CH_3CH_2MgBr} = 8.6 \text{ cps.}$$

suggests that there is nothing anomalous about the effect of the magnesium electronegativity on the vicinal coupling constants, and consequently that (4) may be used to estimate J_t and J_g in bis-(3,3-dimethylbutyl)-magnesium from structurally similar ethanes.

Gutowsky has reported values for J_t and J_g in three halogenated ethanes. These values are summarized in Table II. Note that these values are not the observed coupling constants $< J^{HH} >$ but rather estimates of J_t and J_g obtained from examination of the temperature dependence of $< J^{HH} >$. If J_t for $CHCl_2CHF_2$ is neglected, it seems reasonable to take $J_t \approx 16$ cps. and $J_g \approx 2$ cps. for these halogenated ethanes.

Table II[a]

Vicinal Coupling Constants in Halogenated Ethanes

Compound	J_g	J_t
$CHCl_2CHCl_2$	+2.01	+16.08
$CHCl_2CHF_2$	+2.01	+10.25
$CHCl_2CHFCl$	+1.63, -2.62	+16.5

(a) From reference (32).

Equation (4) suggests that corresponding values for 3,3-dimethylbutylmagnesium chloride should be larger by approximately 1.5 cps. Values of $\underline{J}_t \approx 17.5$ cps. and $\underline{J}_g \approx 3.5$ cps. for $-CH_2CH_2Mg$ are consistent with the value of the average vicinal coupling constant $\langle \underline{J}_{vic} \rangle = \frac{1}{3}(\underline{J}_t + 2\underline{J}_g) =$ 8.1 cps. observed for ethylmagnesium bromide and ethylmagnesium chloride. Using this $\underline{J}_t$ and $\underline{J}_g$ in (2) and (3), one obtains $\chi = 0.75$.

Although too many approximations were involved in obtaining these numbers for them to be of other than qualitative significance, they do suggest that MgX is appreciably larger than a chlorine atom. A more accurate measure of the size of either group could be obtained empirically by comparison with other 3,3-dimethylbutyl compounds bearing substituents of known size.

With these approximate values of $\underline{J}_t$ and $\underline{J}_g$ for bis-(3,3-dimethylbutyl)-magnesium, we are in a position to decide whether changes in the conformational populations I, II and III or change in the rate of inversion at the α-carbon atom is responsible for the variation in the spectra of 3,3-dimethylbutylmagnesium chloride and bis-(3,3-dimethylbutyl)-magnesium with temperature. The separation of the strong outer lines of the room temperature spectrum of bis-(3,3-dimethylbutyl)-magnesium is $(\underline{J}_{13} + \underline{J}_{14})$ and corresponds approximately to 0.75 mole fraction of the <u>trans</u> conformation I. At +110°, the spectrum is a triplet. Abraham and Bernstein have shown that if

$$\underline{J} - \underline{J}' < [2 \Delta \nu_{1/2} (\underline{J}_A - \underline{J}_X)]^{1/2} \qquad (5)$$

the A part of an AA' XX' spectrum will appear as a triplet (36) ($\Delta \nu_{1/2}$ is the width at half-height of the component lines). In the present case, $\Delta \nu_{1/2} = 0.9$ cps. and $\underline{J}_A - \underline{J}_X = 1.2$ cps.; consequently

Equation (5) will be satisfied if $\underline{J}_{14} - \underline{J}_{13} < 1.5$ cps. Assuming that the temperature variation in the spectrum is the consequence of changes in the conformational populations, and substituting $\underline{J}_{14} - \underline{J}_{13}$ into the difference of Equations (2) and (3), one obtains $\chi = 0.40$. This value of χ in Equations (2) and (3) yields vicinal coupling constants of 9.1 cps. and 7.7 cps., and corresponds to a separation of the 1,2 and 3,4 transitions of 16.8 cps. Therefore, if (5) is satisfied, and if changes in rotamer populations are important in determining the appearance of the spectrum, the separation between the outer lines of the α proton spectrum of bis-(3,3-dimethylbutyl)-magnesium should change from 18.0 cps. at room temperature to 16.8 cps. at +110°.

If, on the other hand, an increase in the rate of inversion at the $-CH_2-Mg$ center is responsible for averaging the vicinal coupling constants, it is clear that the separation of these outer lines would remain approximately unchanged (if changes in the relative populations of I, II and III due merely to a change in kT are small).

Experimentally, no significant temperature variation in the separation of the 1,2 and 3,4 transitions is observed. This separation in the spectrum of bis-(3,3-dimethylbutyl)-magnesium remains unchanged at 18.0 $\pm$ 0.2 cps. from +33° to +102°; the corresponding separation in 3,3-dimethylbutylmagnesium chloride changes only from 18.2 $\pm$ 0.1 cps. at +33° to 18.4 $\pm$ 0.3 cps. at -50°.

We believe these data are incompatible with significant temperature dependent variation in populations of the conformers, and conclude that changes in the rate of inversion are responsible for the changes in the spectra of these organometallics.

Organomagnesium compounds derived from halides similar in structure to 3,3-dimethylbutyl chloride show an analogous temperature dependence in their spectra. Thus the spectra of the -CH_2-Mg protons of 3-methylbutylmagnesium chloride and n-butylmagnesium chloride are triplets at room temperature; at -50°, the spectra become more complicated (Fig. 4). The degree of complexity is unfortunately sufficiently great to discourage attempts to analyze the spectra. The 3,3-dimethylbutyl group provides a simple system for analysis, because the four protons of the ethylene fragment are uncoupled to the protons of the t-butyl group. In the 3-methylbutyl- and n-butyl- derivatives however, the chemical shift between the methyl protons and the adjacent methylene protons is of the same order of magnitude as the coupling constant between them, and the α-proton spectrum is consequently complicated (36a).

Although little quantitative information can be obtained from the spectra of these Grignard reagents, or from the spectra of the corresponding dialkylmagnesium compounds (Fig. 5), qualitative comparison with the 3,3-dimethylbutylmagnesium compounds makes clear two similarities in their temperature dependence. The first of these is that the low-temperature spectra of the Grignard reagents are very similar to the room-temperature spectra of the corresponding dialkylmagnesium compounds. The second is that the Grignard reagent spectra do not seem to change at temperatures below approximately -70°, and the dialkylmagnesium spectra change little below +30°.

$(CH_3)_2CHCH_2C\underline{H}_2MgCl$ $CH_3CH_2CH_2C\underline{H}_2MgCl$

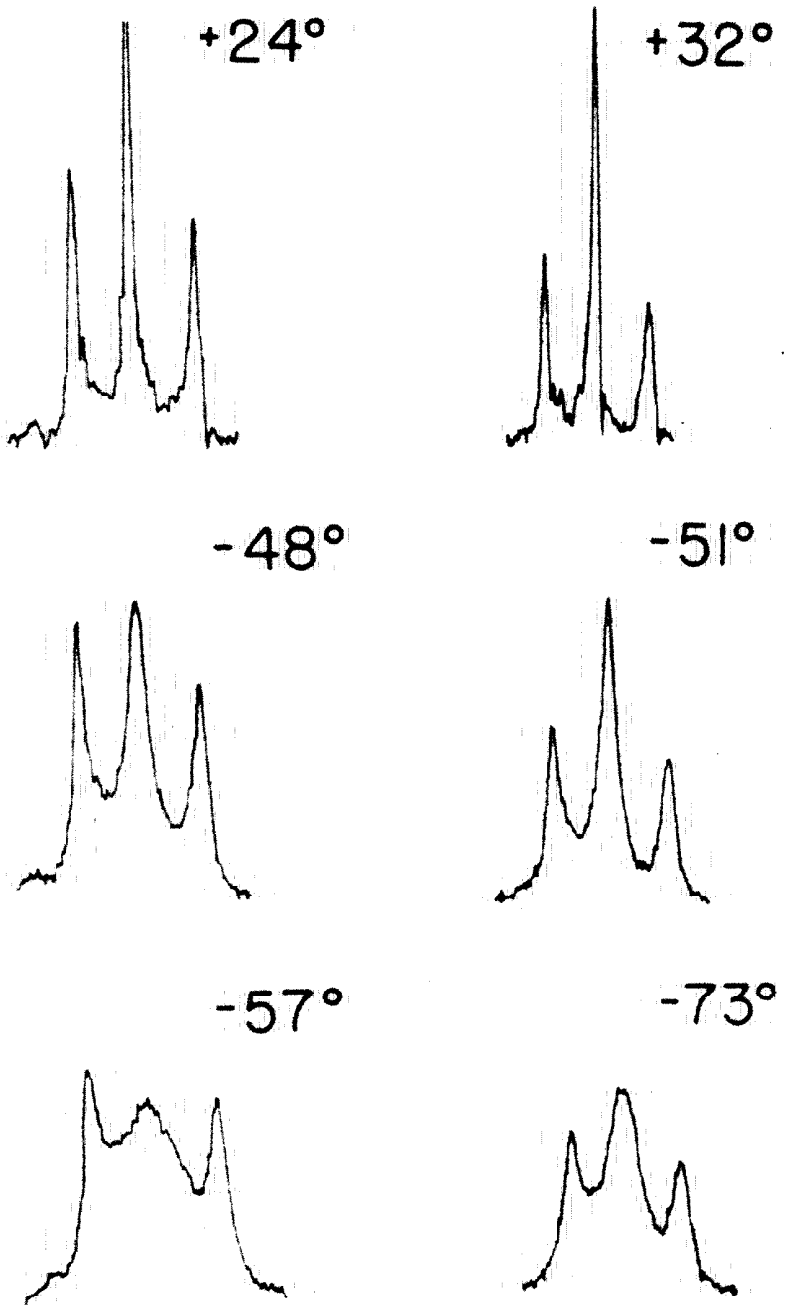


Fig. 4. Spectra of 3-methylbutylmagnesium chloride and n-butylmagnesium chloride in diethyl ether as a function of temperature. Only the spectra of the $\underline{C}H_2$-Mg protons are shown.

Both of these observations are compatible with the explanation previously proposed for the temperature dependence of the spectrum of 3,3-dimethylbutyl Grignard reagent based on the rate of inversion. Moreover, the second of these observations would be difficult to reconcile with important changes in populations of rotational conformations with temperature. If changes in the populations of the trans and gauche conformations were important in determining the temperature dependence of these spectra, the broadening observed in the central line of e.g. di-n-butylmagnesium compared with n-butylmagnesium chloride would be the consequence of an increase in the energy difference between trans and gauche conformations of these compounds. Decreasing the temperature of the Grignard reagent produces a broadening of the central line of its spectrum. If this change were a reflection of changes in conformer populations, lowering the temperature of the dialkylmagnesium compound should result in an analogous change in its spectrum. In fact, little change in the spectrum of the latter compound is observed on decreasing the temperature. Therefore, changes in conformer populations are probably not important in determining the temperature dependence of the spectra.

An analogous argument can of course be applied to the 3-methylbutylmagnesium and 3,3-dimethylbutylmagnesium compounds studied.

The high-temperature spectral behavior of bis-(3-methylbutyl)-magnesium and di-n-butylmagnesium appear comparable with

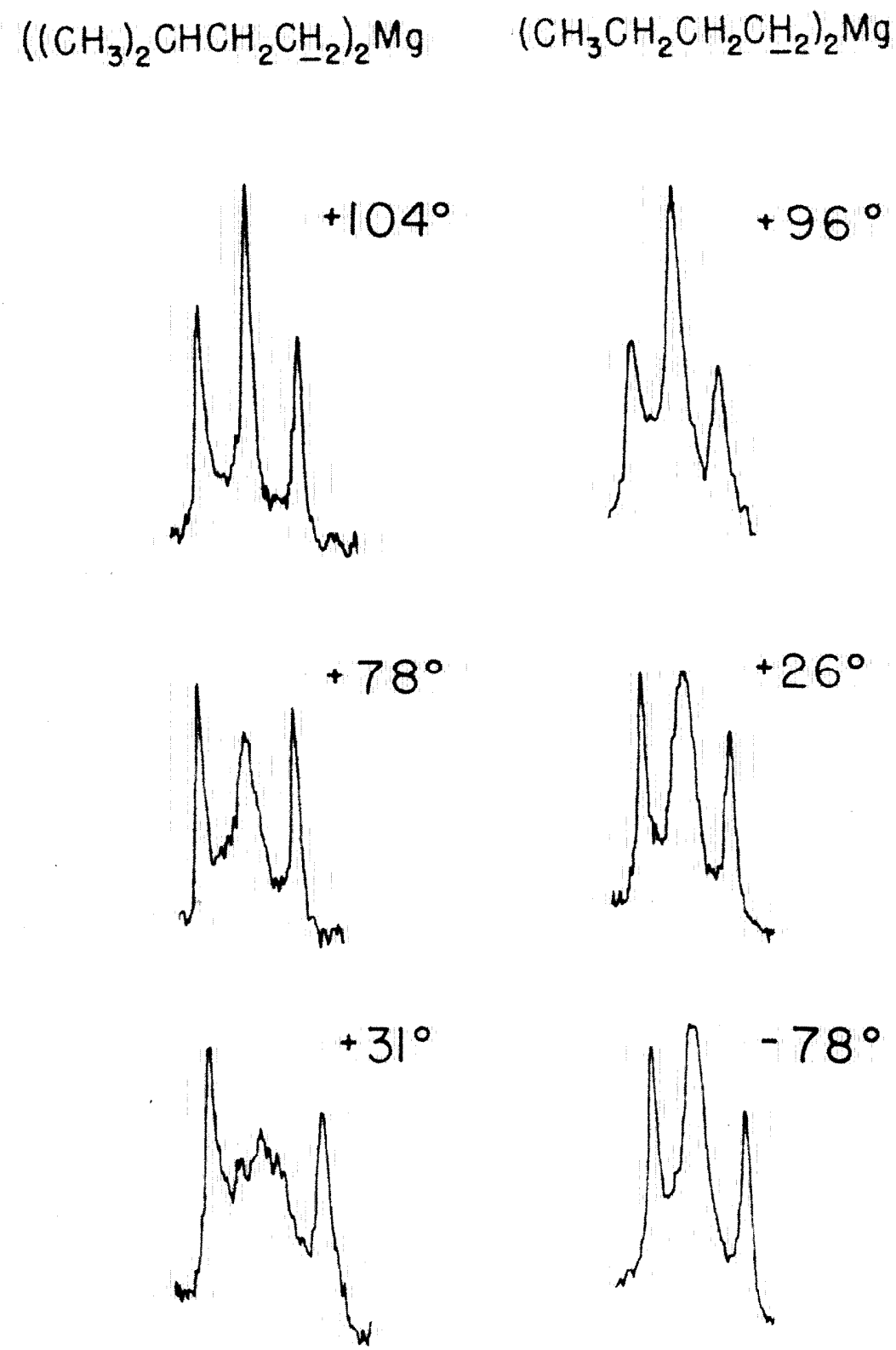


Fig. 5. Spectra of bis-(3-methylbutyl)-magnesium and di-n-butylmagnesium in diethyl ether solution as a function of temperature. Only the spectra of the $\underline{C}H_2$-Mg protons are shown.

that observed for bis-(3,3-dimethylbutyl)-magnesium. Each changes from its "low-temperature" form to a triplet over the temperature range +50° to +110°. Careful measurements of the separation of the outer lines of these compounds were not obtained.

The qualitative similarity in the spectral behavior of these three structurally similar Grignard reagents correspondingly suggests that the rates and thermodynamic parameters for the processes which result in the simplification of their spectra are approximately the same. Although later discussion will demonstrate that changes in structure can markedly affect these parameters, at this point it is of interest to describe briefly certain of the solution variables which have pronounced effects on the rate of inversion at the CH_2-Mg center of the organometallic compound. Those most pertinent are the effects of concentration of the organometallic compound, structure of the solvent and nature of the halogen anion(s) present in solution.

Decreasing the concentration of 3,3-dimethylbutylmagnesium chloride in solution decreases the rate of inversion. Figure 6 indicates that at -8°, a decrease in Grignard reagent concentration of approximately ten-fold changes the spectrum from one characteristic of rapid inversion to one of slow inversion. In these spectra the triplet at lower field is the upfield ether methyl group ^{13}C satellite, and may be used to judge the concentration of the organometallic and the natural linewidth in the solution.

The effect of solvent on the spectrum of the Grignard reagent is equally dramatic (Fig. 7). In diethyl ether solution at room temperature, the spectrum of the -CH_2-Mg protons is a triplet; in

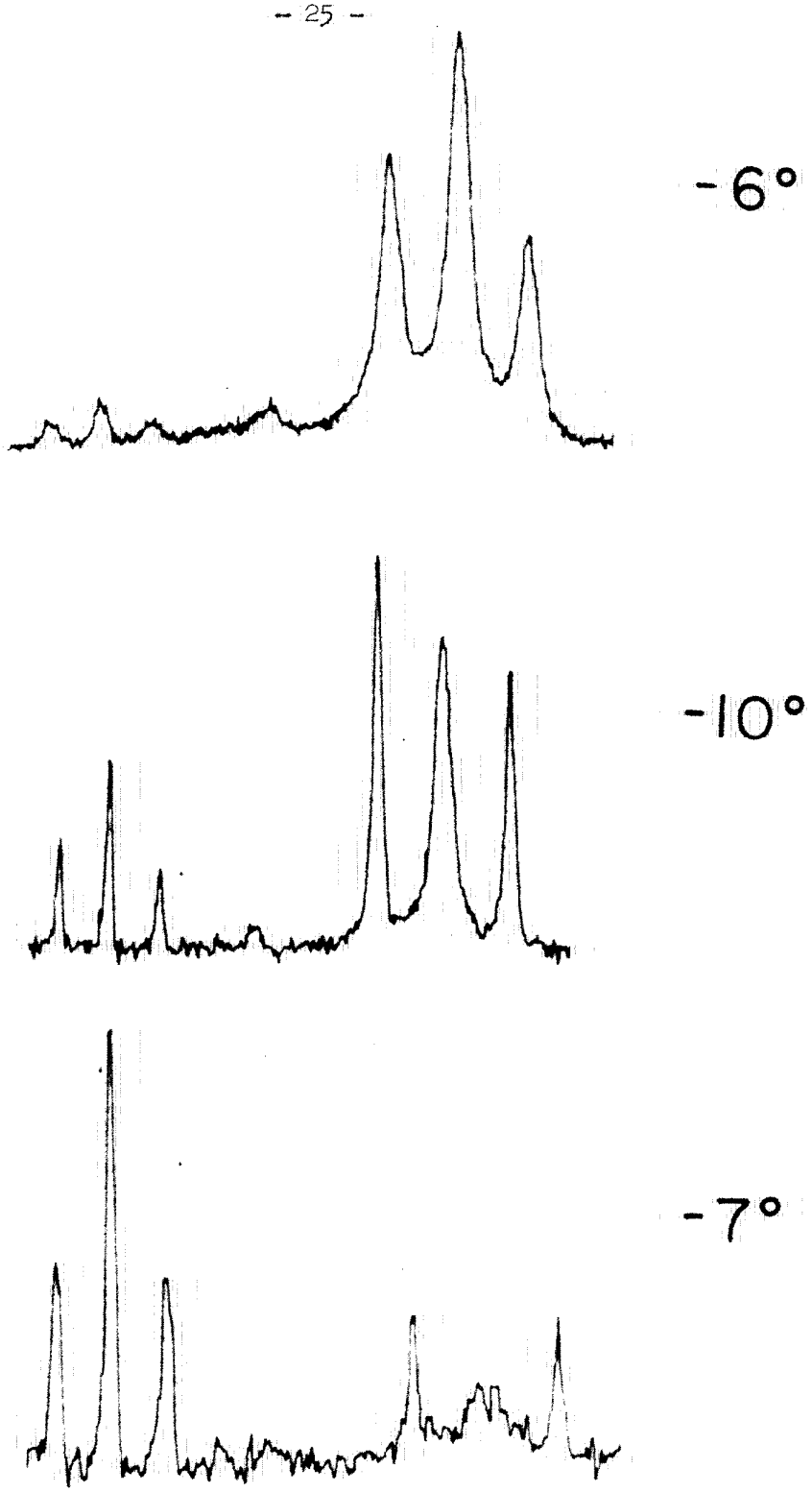


Fig. 6. Spectra of 3,3-dimethylbutylmagnesium chloride in diethyl ether as a function of concentration. The sharp triplet at lower field is the ether methyl ^{13}C satellite.

tetrahydrofuran at approximately the same temperature and concentration, the central line is broadened noticeably; in diglyme, the spectrum is the typical AA'XX' type. The tetrahydrofuran spectrum was examined as a function of temperature and found to collapse to a relatively sharp triplet at +57°. The spectrum became more complicated at temperatures below 0° (unfortunately viscous broadening prevented detailed comparison with the low-temperature diethyl ether solution spectrum). The effect of temperature on the spectrum in diglyme was not examined.

The type and quantity of halide ion present in solution is also important in determining the appearance of the spectrum. In all cases examined, inversion of configuration is slower when bromide ion is the halogen in solution than when chloride ion is present. Thus, the spectrum of 3-methylbutylmagnesium chloride changes from its "high-temperature" triplet to the more complicated "low-temperature" form between -30° and -70°; in contrast, the central line of 3-methylbutylmagnesium bromide shows appreciable broadening at room temperature, and has completed its change to a slow inversion spectrum at -15° (Fig. 8). Qualitatively the same spectral behavior is observed for n-butylmagnesium chloride and n-butylmagnesium bromide respectively.

Addition of magnesium bromide to a solution of 3,3-dimethylbutylmagnesium chloride appears to slow the rate appreciably. A solution prepared by reaction of 0.1 ml. of ethylene dibromide and 0.01 ml. of 3,3-dimethylbutyl chloride with excess magnesium turnings in ether reaches its low-temperature form at -7°; a solution containing the

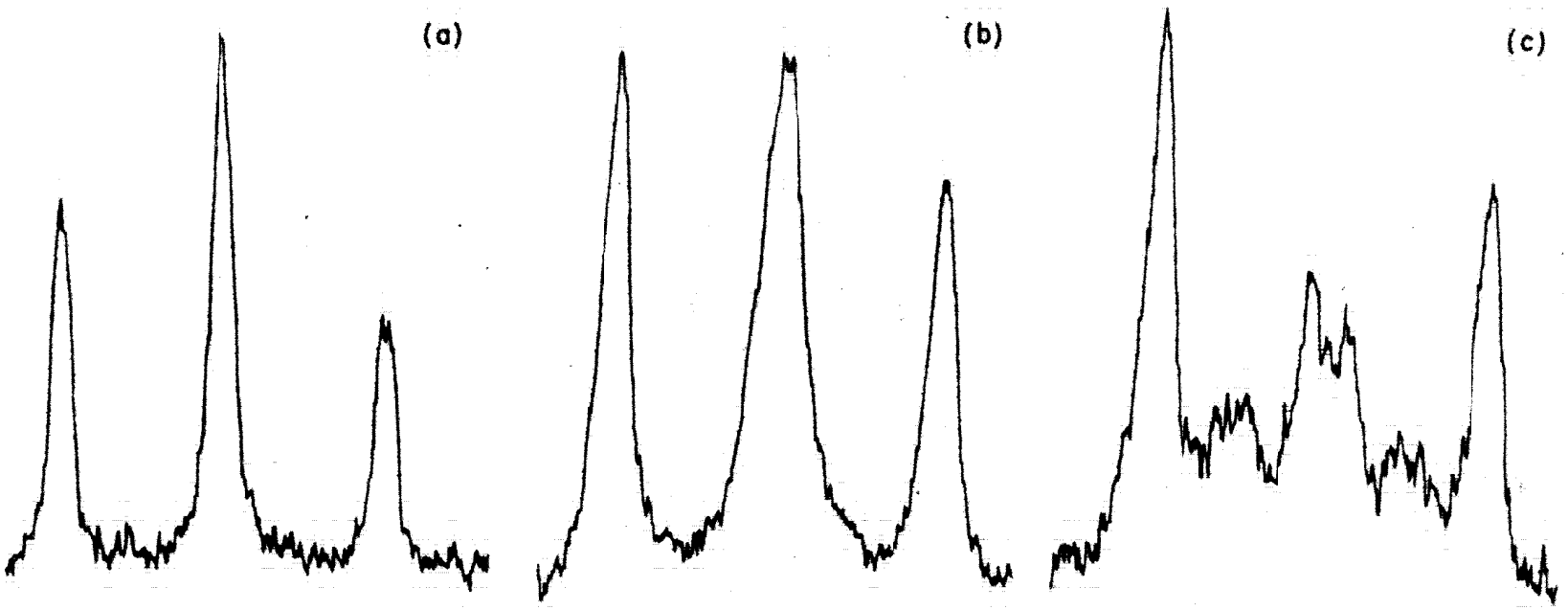


Fig. 7. Spectra of the CH_2—Mg protons of 3,3-dimethylbutylmagnesium chloride as a function of solvent: (a) diethyl ether; (b) tetrahydrofuran; (c) diglyme.

same concentration of Grignard reagent but one-tenth as much magnesium bromide has a corresponding spectrum only at -40°, and the Grignard reagent itself has this spectrum at approximately -50° (Fig. 9).

These last experiments indicate that halide ion is probably involved in some specific manner in the rate determining step for the process averaging the vicinal coupling constants. That is, the effect of the halide ion is not merely to influence properties of the solution such as dielectric constant or ionic strength, but rather to change the activation energy for the inversion process by its effect on the structure or solvation of the organometallic compound. It might be possible in the absence of these observations to rationalize the decrease in rate of inversion with decreasing concentration as the result purely of changes in the bulk properties of the solution. In particular, if the transition state for inversion involves charge

$$\overset{\delta-}{RCH_2} \cdots \overset{\delta+}{Mg} \cdots$$

separation the dielectric constant of the solvent will be important in determining the rate.

Dessy and Jones have examined the dielectric constant of solutions of ethylmagnesium bromide and of diethylmagnesium and found a pronounced concentration dependence (25). Their values are reproduced in Table III.

The concentration of the Grignard reagent in solutions used for n.m.r. samples was ordinarily 0.2 M to 3 M. If the samples examined by Dessy are a fair model, the solution dielectric constant in this concentration range should be quite sensitive to changes in

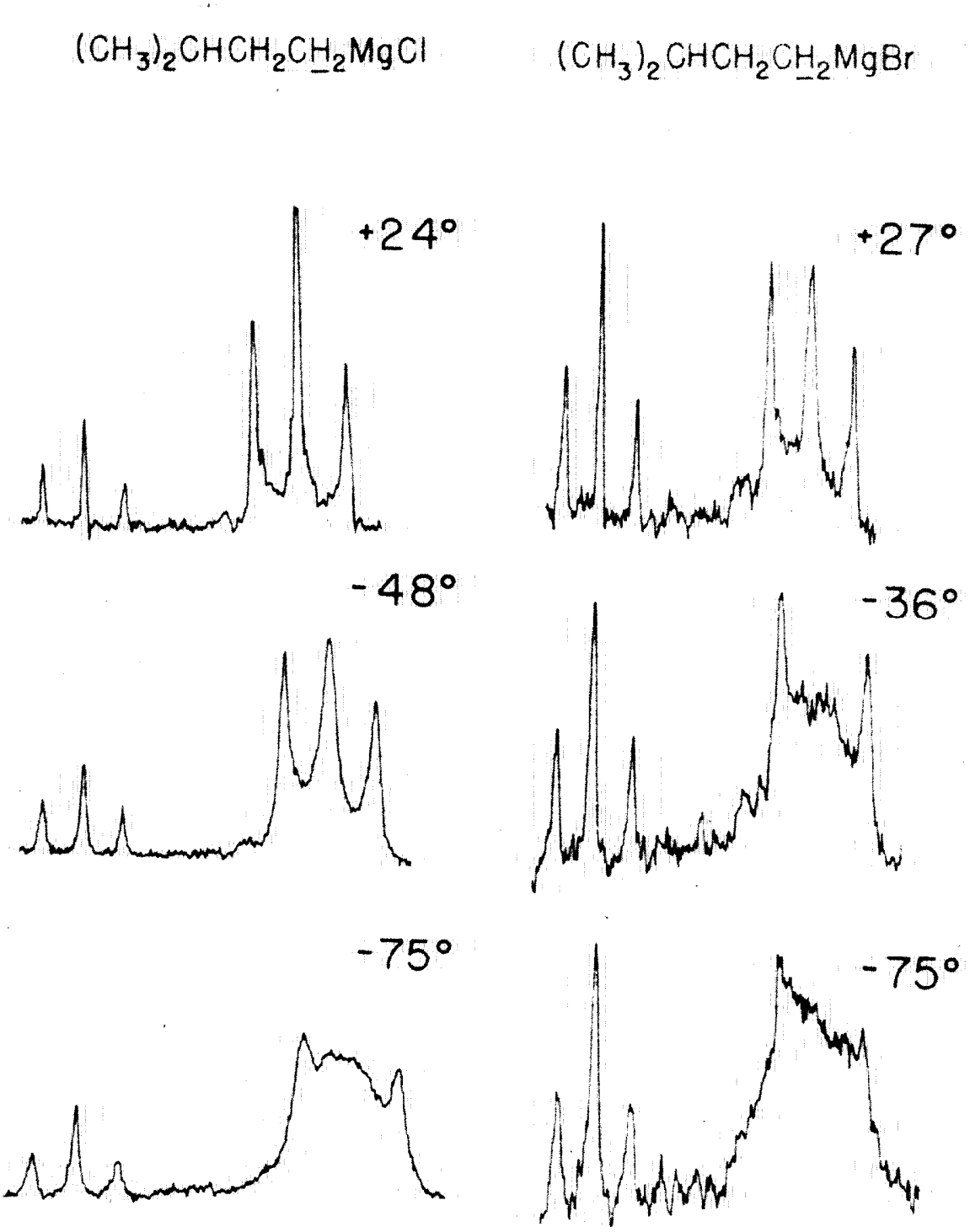


Fig. 8. Spectra of 3-methylbutylmagnesium chloride and 3-methylbutylmagnesium bromide in diethyl ether solution as a function of temperature. The sharp triplet at low field in each spectrum is the ^{13}C satellite of ether. Note that the concentration of the two organometallic compounds is significantly different.

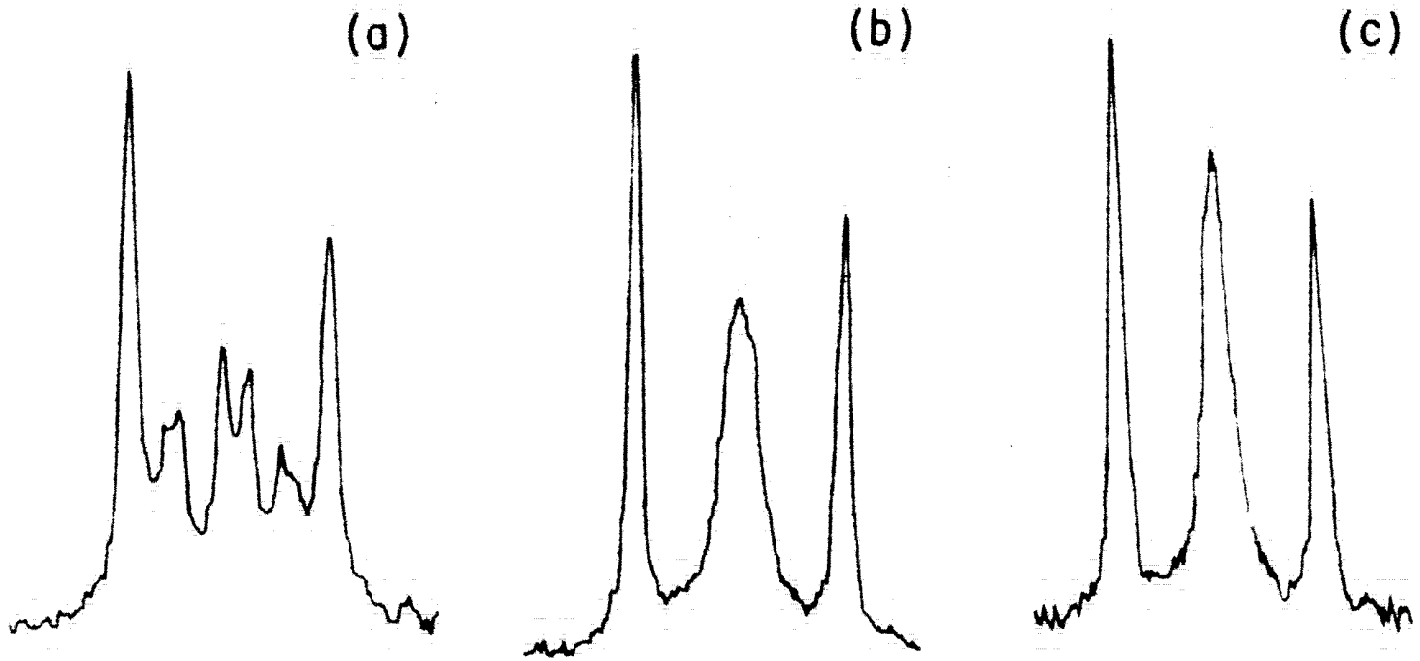


Fig. 9. Spectra of 3,3-dimethylbutylmagnesium chloride in diethyl ether at -7° as a function of added magnesium bromide. The approximate molar ratios of magnesium bromide to 3,3-dimethylbutylmagnesium chloride in the solutions are: (a) 1.5; (b) 0.15; (c) 0.00.

Table III[a]

Dielectric Constants of Ether Solutions of Ethylmagnesium Bromide (I) and Diethylmagnesium (II)

Concentration	Dielectric Constant	
	I	II
0.125 M	5.1	4.6
0.250	6.5	5.3
0.500	11	6.6
1.000	35	11

(a) From reference (25).

concentration. Consequently, the ten-fold change in concentration in the samples in Figure 6 might have been accompanied by a five-fold change in dielectric constant. A decrease in dielectric constant of this magnitude would significantly decrease the rate of a process depending primarily on charge separation.

However, addition of magnesium bromide to a Grignard reagent solution can reasonably be expected to increase the dielectric constant of the solution (25). If dielectric constant were the most important factor in determining the rate of inversion of 3,3-dimethylbutylmagnesium chloride, the order in Figure 9 should be the opposite of that observed.

It is important to notice that the spectrum observed for solutions containing both chloride and bromide ion is not a superposition of the spectra of two separate species "RMgCl" and "RMgBr" but rather an average spectrum. Similar averaging is also observed in mixtures

of dialkylmagnesium and magnesium halide in ether. If, for example, a solution of 3,3-dimethylbutylmagnesium chloride is treated with less than a stiochiometric amount of dioxane, the magnesium chloride present in solution is only partially removed. The spectrum observed for such a solution is not a superposition of the spectra of the Grignard reagent and the dialkylmagnesium compound separately, but an averaged spectrum. Correspondingly, addition of an excess of magnesium bromide to a solution of bis-(3,3-dimethylbutyl)-magnesium produces a sample whose vicinal coupling constants are averaged; addition of less than a stoichiometric amount of magnesium bromide results in partial averaging.

These observations suggest that the species involved in the Schlenk equilibrium, "RMgX," "R_2Mg" and "$R_2Mg \cdot MgX_2$" do not have prolonged separate existence in solution. It is not presently possible to decide whether the partial averaging of vicinal coupling constants observed for samples containing less than a stiochiometric quantity of magnesium chloride is the result of rapid migration of halide ion from magnesium to magnesium, of rapid migration of magnesium chloride as a separate species, or of some other process occurring in solution.

Discussion of the Grignard reagents considered up to this point has centered on the observation of a temperature dependent averaging of vicinal coupling constants between α and β methylene protons. The same kind of information can in principle be obtained from chemical shift data. In suitably chosen systems such data can be treated quantitively with less difficulty than can those derived from coupling constant measurements. The two primary Grignard

reagents examined for evidence of chemical shift averaging were selected in the expectation that their α-methylene group would have an AB type spectrum if inversion at the -CH_2-Mg center were slow, and an A_2 type spectrum if inversion were rapid.

The protons of a methylene group removed by one or more bonds from a center of molecular asymmetry may be magnetically non-equivalent and display AB type n.m.r. spectra (37). Recent investigations of this subject have established that conformational preference is responsible for the major part of the magnetic non-equivalence of the methylene protons (37d,38). A primary Grignard reagent which might be expected to have magnetically non-equivalent methylene protons would thus be one in which one rotational conformation around the α-β carbon-carbon bond would be significantly lower in energy than the other two. The CH_2-Mg protons of two Grignard reagents, 2-phenylpropylmagnesium bromide and 2-phenyl-3-methylbutylmagnesium chloride were examined for evidence of magnetic non-equivalence. The α-methylene hydrogens of the former in diethyl ether solution had an A_2-type spectrum from +33° to -80° (viscous broadening prevented measurement below this temperature). The methylene protons of the latter had a spectrum characteristic of the AB part of an ABX spectrum at room temperature; at +110°, the spectrum collapsed to an A_2X type (Fig. 10).

The proposed interpretation of the temperature dependence of 2-phenyl-3-methylbutylmagnesium chloride is the same as that for 3,3-dimethylbutylmagnesium chloride. The magnetic non-equivalence of the methylene hydrogens at +33° demonstrates clearly that inversion of configuration at the -CH_2-Mg center is slow on the n.m.r.

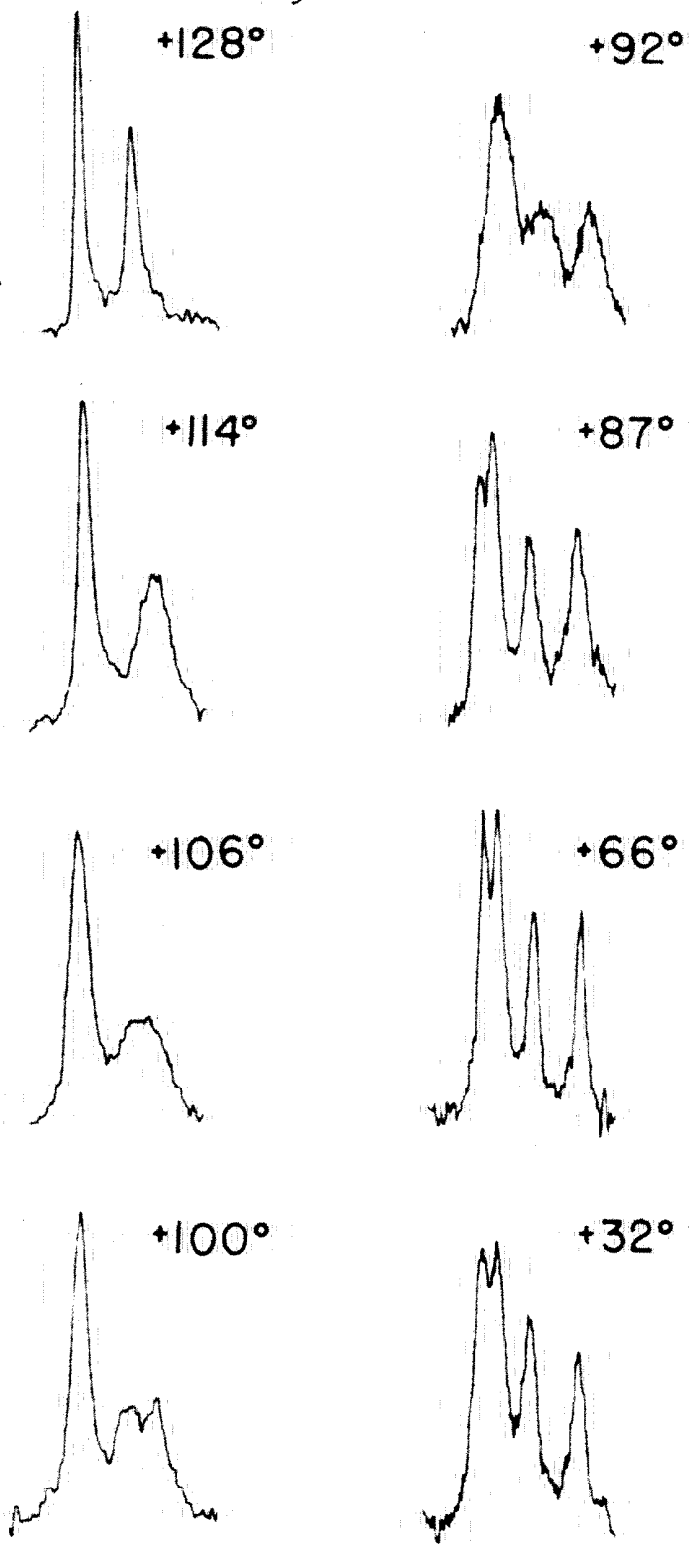


Fig. 10a. Spectra of the CH_2-Mg protons of 2-phenyl-3-methylbutylmagnesium chloride in tetrahydrofuran as a function of temperature.

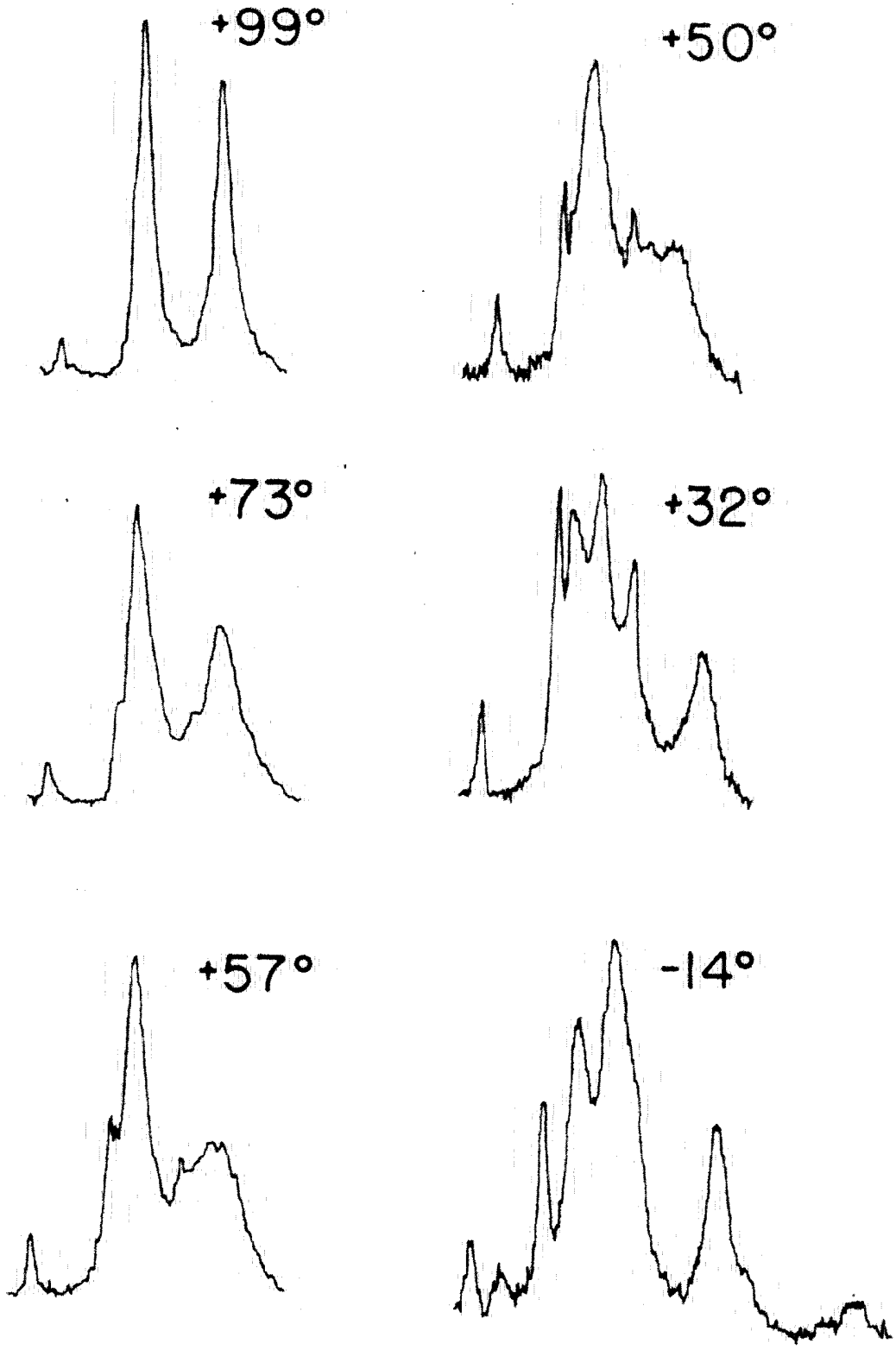


Fig. 10b. Spectra of the CH_2-Mg protons of 2-phenyl-3-methylbutylmagnesium chloride in diethyl ether, as a function of temperature. The spectrum of the organometallic compound is superimposed on that of the ether ^{13}C satellite.

time scale. The collapse of the magnetic non-equivalence as the temperature is increased is taken as evidence that a rapid inversion of configuration, analogous to that proposed previously, averages the magnetic environments of the methylene hydrogens.

The quantitative discussion of this spectrum is less convincing than that of the spectra of the 3,3-dimethylbutylmagnesium derivatives, because the chemical shifts and coupling constants obtained on analysis have much greater uncertainty. The AB part of an ABX spectrum has eight theoretical lines, of which four are of low intensity. The position of the low intensity lines is uncertain in the room temperature spectra of both 2-phenyl-3-methylbutylmagnesium chloride and bis-(2-phenyl-3-methylbutyl)-magnesium. These lines are necessary for accurate determination of the geminal methylene coupling constant, and the magnitude of this coupling constant is consequently rather uncertain. The spectrum is further confused by the accidental near-degeneracy of two of the intense lines. Moreover, no information can be obtained from the X part of the spectrum, due both to its low intensity and to its complexity.

Therefore, although agreement can be obtained between the observed and calculated spectra, the values obtained from analysis cannot be regarded as highly precise. Coupling constants and chemical shifts for a solution of this Grignard reagent in diethyl ether solution at -14°, and in tetrahydrofuran solution at +33, and for the corresponding dialkylmagnesium compound in ether at +33° are reported in Table V. The starting halide has an A_2X type spectrum in carbon tetrachloride solution.

Table V

Spectral Parameters for the Methylene Protons of 2-Phenyl-3-Methylmagnesium X Treated as an ABX System[e]

	X = Cl[a]	X = Cl[b]	X = R[c]
$\nu_A - \nu_B$	12.9	9.2	14.2
$\nu_A - \nu_X$[d]	150	150	150
$\underline{J}_{AB}$	-12.2	-12.5	-12.2[d]
$\underline{J}_{AX}$	10.3	9.7	10.2
$\underline{J}_{BX}$	4.3	5.6	3.2

(a) Diethyl ether solution at -14°.

(b) Tetrahydrofuran solution at +33°.

(c) Diethyl ether solution at -14°.

(d) This value was assumed.

(e) Accuracy in the coupling constant values is estimated to be $\pm$ 0.3 cps.

It is possible to discuss the temperature dependence of this Grignard reagent in the same manner used for 3,3-dimethylbutylmagnesium chloride. If an increase in the rate of inversion of configuration is responsible for the averaging of the vicinal coupling constants observed at high temperature, $< \underline{J}^{HH}_{vic} >$ should be equal to $1/2(\underline{J}_{AX} + \underline{J}_{BX})$. If large changes in conformational populations are responsible (such changes also averaging the chemical shifts of the methylene hydrogens), $< \underline{J}^{HH}_{vic} >$ should deviate significantly from the average of the room temperature coupling constants.

The values reported for the vicinal coupling constants in Table V are not sufficiently accurate to justify a calculation of the magnitude of the difference between the high temperature vicinal coupling constant and the average of the two low temperature vicinal coupling constants, assuming that changes in rotational conformation populations do determine the appearance of the spectra. Consequently, the degree of experimental uncertainty which is tolerable in this discussion is unknown. Nonetheless, the observed vicinal coupling constant at high temperature is 7.6 ± 0.3 cps., and the average $1/2(J_{AX} + J_{BX})$ is 7.3 ± 0.3 cps.; the two numbers are the same within experimental error.

We conclude that inversion at the CH_2-Mg center occurs in this Grignard reagent as in the primary Grignard reagents discussed previously.

By contrast, the α methylene hydrogens of 2-phenylpropylmagnesium bromide are magnetically equivalent over the temperature range +33° to -80° (viscous broadening again prohibits observations below this limit). Fraenkel and co-workers have suggested that the observation of an A_2 type spectrum indicates that this Grignard reagent is inverting rapidly at room temperature (39). However, we have examined the spectrum of bis-(2-phenylpropyl)-magnesium at -75°, and find that the methylene protons of the dialkylmagnesium are still magnetically equivalent. The preceding discussions have demonstrated clearly that other, structurally similar dialkylmagnesium compounds invert at a rate rapid enough to influence their spectra only at temperatures above -50°. There is no obvious

reason why the rate of inversion of bis-(2-phenylpropyl)-magnesium should be anomalous. We believe that this dialkylmagnesium is inverting slowly, but that its asymmetric center is not of the correct type to produce a significant magnetic non-equivalence in the methylene protons. Therefore, no conclusions can be drawn about the rate of inversion of 2-phenylpropyl Grignard reagent from its n.m.r. spectrum.

The results discussed so far have dealt entirely with primary Grignard reagents. Although a limited number of examples have been examined, these results define clearly the rates of inversion which may be expected for this class of organometallic compound.

A comparison of the rate of inversion of suitably chosen primary and secondary Grignard reagents might be expected to be useful, in light of the probably pertinence of such data to considerations of the mechanism of inversion. Unfortunately application of the techniques used in examination of the primary Grignard reagents to several secondary Grignard reagents has been less successful. It has not proved possible to measure the rate of inversion of a secondary Grignard reagent; however it is possible to establish a lower limit on this rate from the experiments described below.

The spectrum of the Grignard reagent prepared from 3,3-dimethylcyclobutyl bromide in tetrahydrofuran solution at room temperature shows a doublet for the methyl protons (Fig. 11). The magnetic non-equivalence of the methyl groups can reasonably be explained only as the consequence of slow inversion of configuration at the C<u>H</u>-Mg

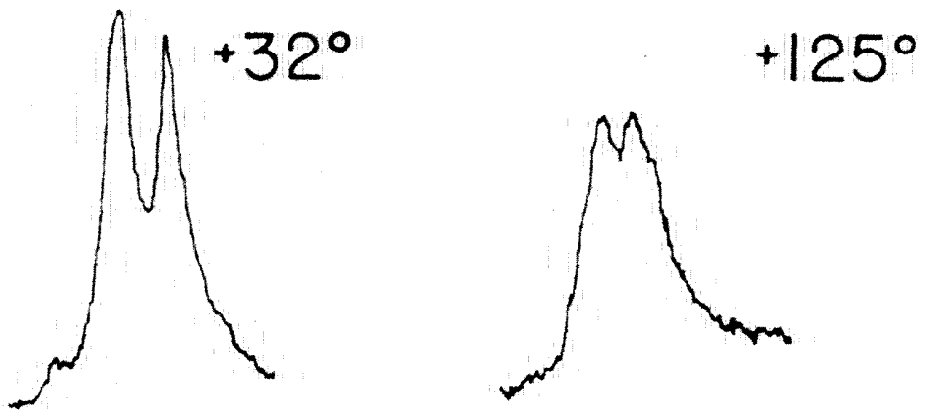


Fig. 11. Spectrum of the methyl protons of 3,3-dimethylcyclobutylmagnesium bromide in tetrahydrofuran. The separation between the two peaks is approximately 4 cps. at +32.

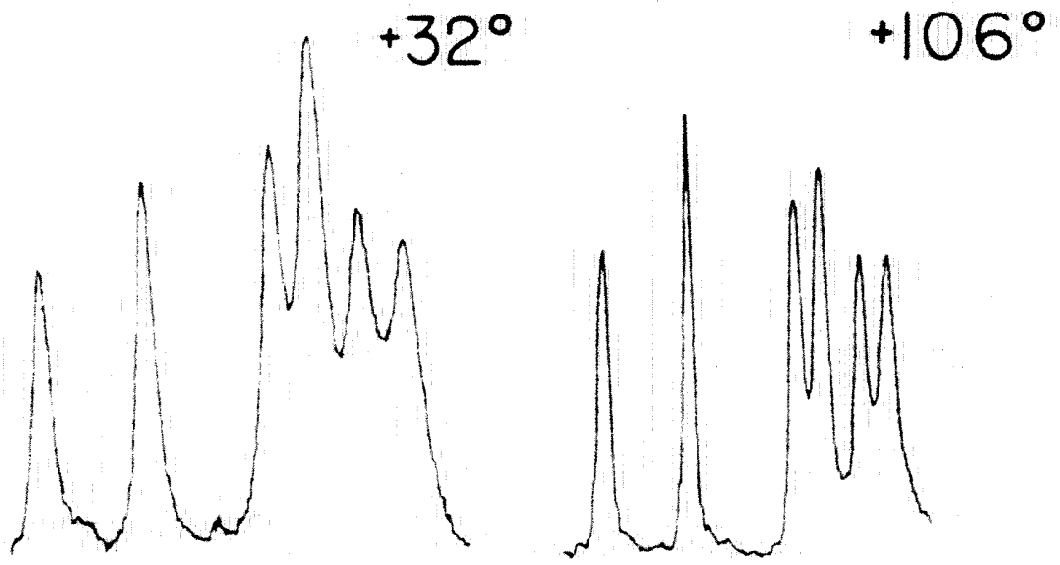


Fig. 12. Spectrum of the methyl protons of 3-methylbutylmagnesium chloride in tetrahydrofuran solution. The four lines at highest field are the isopropyl methyl proton resonances.

center. In a slowly inverting Grignard reagent, two types of methyl groups are present; one cis to the magnesium atom, one trans. The absence of a chemical shift between the two methyl groups would not have allowed an unambiguous interpretation, because either rapid inversion of configuration at the CH-Mg center or an accidental degeneracy of the chemical shifts in a slowly inverting Grignard would give the same result. However, the observation of two kinds of methyl protons indicates clearly that inversion is slow in this molecule.

Similarly, the two isopropyl methyl groups of 2,3-dimethylbutyl Grignard reagent are magnetically non-equivalent at room temperature in both tetrahydrofuran and deuterodiethyl ether solution (Fig. 12). The carbon atom bearing the magnesium atom in this compound is a center of molecular asymmetry. The observation that the adjacent isopropyl methyl groups are magnetically non-equivalent indicates that inversion of configuration at the -CH-Mg center is slow on the n.m.r. time scale (cf. Part II of this thesis).

Neither of these compounds shows significant temperature dependence in its spectrum. The chemical shift between the methyl protons of 3,3-dimethylbutylmagnesium bromide does not change over the temperature range +33° to +120°. The chemical shift between the methyl protons in the isopropyl group of 2,3-dimethylbutylmagnesium chloride does decrease by approximately 0.7 cps. between +33° and +120°; however, this decrease occurs gradually over the indicated temperature range, and is probably due to changes in the rotational conformation populations of the isopropyl group rather than to a change in the rate of inversion.

The absence of a significant temperature dependence in the spectra of these two compounds suggests that the barrier to inversion of configuration is higher in the secondary than in the primary Grignard reagents. It might be argued that 3,3-dimethylcyclobutyl Grignard reagent is not a representative secondary Grignard reagent, since the ring strain of the molecule and hybridization of the carbon atoms are atypical. However, 3,3-dimethylbutyl Grignard reagent seems a reasonable model for a secondary Grignard reagent.

This order of configurational stabilities is not surprising, if the carbanionic character of the alkyl group is more pronounced in the transition state for inversion than in the ground state of the molecule, because the generally greater stability of primary carbanions relative to secondary carbanions (39a) would suggest a higher activation energy for inversion of secondary than primary Grignard reagents.

It should be noted in this connection that reaction of a dialkylmercurial with mercuric bromide proceeds at the same rate for diisopropyl- and di-n-propylmercury compounds and faster for dicyclopropylmercury and diphenylmercury (40). This dissimilarity between the influence of the alkyl group on the rate of this reaction and on that of the Grignard inversion suggests that the well-established S_E2 mechanism for the mercurials and the mechanism of inversion in the Grignard reagents are probably not closely related.

It seems probable that rates fast enough to study by the techniques used for primary Grignard reagents cannot be expected in

normal secondary Grignard reagents (i.e., Grignard reagents lacking special stabilization of the carbanionic center). It should be possible to increase the rate of inversion sufficiently to apply these techniques by stabilizing the carbanionic center, perhaps by conjugation. However, any conclusions drawn from comparison of a secondary Grignard reagent of this type with a normal primary Grignard would be of limited generality. It therefore seemed important to find a method of spectroscopically determining the inversion rate for the "slowly-inverting" secondary Grignard reagents.

The one attempt which has so far been made to utilize n.m.r. spectroscopy for examination of a slowly inverting Grignard reagent was unsuccessful. This experiment will nonetheless be described briefly, because it appears a potentially useful technique for examination of slow reversible reactions by n.m.r. spectroscopy.

The Grignard reagent of 1-chloro-2-methylcyclopentane-2-^{2}H was prepared and its spectrum examined in tetrahydrofuran solution. In principle, this organometallic should exist as a mixture of two stereoisomers: one in which the magnesium atom is trans to the methyl group, and one in which it is cis. If inversion of configuration occurs in this Grignard reagent, an equilibrium will be established between the concentrations of the two isomers. These equilibrium concentrations should be temperature dependent, since the cis- and trans- isomers should be of different energy.

If the isomeric composition of a sample of Grignard reagent is allowed to reach equilibrium at one temperature, and the temperature

is then changed, it should be possible to determine the rate at which equilibrium is re-established by measuring the rate of change of the intensities of the spectra of the two stereoisomers. Measurement of this rate would constitute a direct determination of the rate of inversion of configuration at the metal-bearing carbon atom.

This experiment clearly requires that three conditions be satisfied if it is to be successful. First, the cis- and trans- isomers must give distinct signals. Second, there must be appreciable concentrations of both isomers in solution. Third, the isomers must be in equilibrium. Unfortunately, few data are available which might serve to guide the construction of a Grignard reagent fulfilling these conditions. It is however encouraging that Sauers and Kwiatkowski (41) have examined the products from carbonation of 2-norbornylmagnesium bromide as a function of temperature, and have found that the ratio of exo- to endo- acids varied from 9:1 at -78° to 7:3 at +25° (42). These experiments may merely reflect a difference in activation energy for endo and exo carbonation; they may also reflect a temperature dependent equilibrium between endo- and exo-norbornyl Grignard reagent.

The proposed experiment seems practical; the particular Grignard reagent chosen did not yield the desired information. The α-proton resonance was broad but symmetrical; the methyl resonance was a single peak, somewhat broadened by spin-coupling with the deuterium, superimposed on several smaller peaks. The spectrum showed no change after heating or cooling.

The most probable explanation of the failure of this experiment is that appreciable concentration of only one of the two stereoisomers (presumably the trans isomer) exists in a solution of this Grignard reagent. Probably 2-phenyl-2-methylcyclopentylmagnesium chloride, in which the energy difference between the cis- and trans- isomers would be small, or even norbornyl Grignard reagent would stand a better chance of success in an experiment of this type.

CALCULATIONS

The application of n.m.r. spectroscopy to the measurement of chemical rate processes in liquids is based on the study of resonance line shapes and positions. In most instances, spectra are obtained under conditions in which the region of interest in the spectrum is swept slowly (so-called slow-passage conditions) and only such experiments will be considered in this section.

The simplest kinetic problem which can be treated by n.m.r. is that of measuring the rate at which protons exchange between two equally populated sites of different chemical shift, under conditions in which spin-spin coupling between the protons is zero; the only simpler exchange problem, that of uncoupled protons exchanging between sites of the same chemical shift, is not interesting, because such exchange has no effect on the appearance of the spectrum.

The general exchange behavior of this simple system is well known. Qualitatively, when the exchange rate is slow and the average life-time τ of a proton at one site is consequently large compared with the difference in chemical shift δ between the sites, the spectrum consists of two sharp lines of equal intensity separated by δ. When exchange is sufficiently rapid that τ is small compared with δ, only one line is observed, occurring midway between the two observed when $\tau > \delta$. When τ and δ are of the same order of magnitude, the spectrum consists of two broadened lines, with separation less than δ.

General mathematical descriptions of the spectra in the region of intermediate exchange rate have been devised by several workers (43).

The starting point for most of these calculations has been the Bloch equations, either in their original form (44) or in the modified form proposed by McConnell (45).

These treatments have been extended in some cases to include exchange broadening of spin-spin multiplets, by considering the observed spectrum to be the superposition of several independently exchanging doublets: each line in the spin multiplet is assigned an "effective chemical shift" equal to the chemical shift between the two sites in the absence of spin-spin coupling plus or minus the appropriate multiple of the coupling constant. The corresponding Bloch equations are then solved independently for each of these doublets (44a,46). A treatment of this type has been applied successfully to the examination of proton exchange between methylammonium ion and water (46).

Unfortunately such treatments are not easily extended to many of the cases of interest to organic chemists, in which the chemical shifts between exchanging protons may be of the same order of magnitude as the coupling constants between them.

An alternative approach to the problem of exchange broadening has been suggested by Kaplan (47) and developed in detail by Alexander (48). This treatment is based on the equations of motion of the nuclear spin-density matrix for the spin system under consideration. Its application to simple coupled systems is less complicated than treatments based on the Bloch equations. Moreover, if certain drastic approximations are made in the calculations, it is possible to obtain crude but useful information from more complicated systems.

Alexander's papers are unfortunately phrased in terms that are unfamiliar to the average organic chemist, and are presented in outline form unsuited for application to practical problems. Therefore, it seems useful to recapitulate in less technical terminology some of the arguments used in Alexander's treatment, and to provide the details of a simple illustrative calculation, before discussing the more complicated exchange dependence of the Grignard reagent spectra. It should be emphasized that the treatment discussed is basically unchanged from that presented in Alexander's paper.

To make our discussion more concrete, specific details of the calculations involved in this treatment of exchange broadening will be illustrated as they arise by explicit calculation for a simple AB type system. Extension to the more complicated Grignard reagent spectra will be examined separately. Before beginning these calculations, it will be necessary to introduce the concept of the "density matrix" ρ (49).

The usual approach to the analysis of the n.m.r. spectrum of a molecule in an applied magnetic field consists of two distinct parts. In the first part, the energies of the interactions between the individual magnetic moments of the nuclei in the molecule and their magnetic environments are calculated, and used to construct an energy-level diagram for the nuclear spin system of the molecule in the applied static field. In the second part, the probabilities of transitions between these energy levels due to a weak magnetic field rotating at a frequency close to the Larmour frequency of the nuclei,

in a plane perpendicular to the main static field, are calculated and used to construct a theoretical spectrum.

For protons, the two most important contributors to the magnetic field seen at the nucleus are the static external field (giving rise to field-dependent chemical shift-type interactions) and local internal fields originating in the magnetic moments of the other nuclei in the molecule (spin-spin interactions). In order to calculate the magnitude of the interaction of a system of nuclei with magnetic fields of these types it is necessary to know both the form of the appropriate Hamiltonian operator $\tilde{\mathcal{H}}$, and the possible nuclear spin wave functions Ψ_n for the spin system being considered. We will defer discussion of the Hamiltonian until the discussion of the density matrix has been completed.

The nuclear spin wave functions Ψ_n describe completely the behavior of the spin system under examination. These functions can be expanded in terms of a complete set of time-independent orthonormal functions

$$\Psi_n = \sum_j c_{nj} \phi_j \qquad (1)$$

For the problem of an AB spectrum the functions ϕ_j will be the four basic product functions

$$\phi_1 = \alpha(1)\alpha(2) \qquad (2a)$$

$$\phi_2 = \alpha(1)\beta(2) \qquad (2b)$$

$$\phi_3 = \beta(1)\alpha(2) \qquad (2c)$$

$$\phi_4 = \beta(1)\beta(2) \qquad (2d)$$

Here, $\alpha(1)\beta(2)$ indicates that $I_z(1)$, the component of spin angular momentum of nucleus 1 along the direction of the applied field, is $+\frac{1}{2}$, and $I_z(2) = -\frac{1}{2}$. This choice of basis functions is of course not unique. Any other set of four orthonormal functions which could be constructed from (2) would serve equally well. For example, another possible set would be

$$\phi_1 = \alpha(1)\alpha(2) \tag{3a}$$

$$\phi_2 = 1/\sqrt{2}(\alpha(1)\beta(2)+\beta(1)\alpha(2)) \tag{3b}$$

$$\phi_3 = 1/\sqrt{2}(\alpha(1)\beta(2)-\beta(1)\alpha(2)) \tag{3c}$$

$$\phi_4 = \beta(1)\beta(2) \tag{3d}$$

However, every possible basis set will not be equally convenient for computational purposes, although the final spectrum calculated will be independent of the choice of basis set.

For a state of the spin system represented by the wave function Ψ_n, the value of some observable property of the system, for example the magnetization $< I_x + iI_y >$ in the plane perpendicular to the applied field may be written

$$< I_x + iI_y >_n = < \Psi_n^* \mid \underset{\sim}{I}_x + i\underset{\sim}{I}_y \mid \Psi_n > \tag{4}$$

where $\underset{\sim}{I}_x$ and $\underset{\sim}{I}_y$ are operators giving the component of the total spin angular momentum along the x and y axes respectively, Ψ_n^* is the complex conjugate of Ψ_n, and $i = \sqrt{-1}$. The reason we choose here the particular operator $\underset{\sim}{I}_x + i\underset{\sim}{I}_y$ for illustrative purposes is that $< I_x + iI_y >$ is the property of the spin system actually observed in an n.m.r. experiment. The geometry of the sample with respect

to the applied fields is ordinarily defined so that the z direction lies along the static field H_o. The sample is irradiated with a radio-frequency field H_1 rotating in the x-y plane, and the magnetization induced in the sample in this plane is measured by receiver coils perpendicular to the transmitter coils. The induced magnetization is written as $< I_x + iI_y >$ rather than $< I_x - iI_y >$ because the former corresponds to a magnetization induced in the sample as a result of $\Delta F_z = +1$ transitions (i.e. resonance <u>absorption</u> of energy from the radio-frequency field) while the latter corresponds to emission induced by the field.

Expanding the wave functions Ψ_n in (4) in terms of the basis set ϕ_j, and calling $\underset{\sim}{I}_x + i\underset{\sim}{I}_y$ the "raising operator" $\underset{\sim}{I}^+$

$$< I_x + iI_y >_n = < \sum_j c^*_{nj}\phi^*_j \left| \underset{\sim}{I}^+ \right| \sum_k c_{nk}\phi_k >$$

$$= \sum_{j,k} c_{nk}c^*_{nj} \, (\phi^*_j \mid \underset{\sim}{I}^+ \mid \phi_k) \qquad (5)$$

This description is adequate for one molecule. An n.m.r. sample, however, consists of a very large number of molecules, only some of which will be described by the wave function Ψ_n, while others will be described by other wave functions $\Psi_m, \Psi_l, \cdots$. All of these functions can of course be expanded in terms of the basis set ϕ_j, because the basis set was defined as complete. The value of the magnetization in the x-y plane which will actually be measured for a real sample will be the sum of the contributions from each of the individual molecules. If we assign a statistical weight p_n to the molecules

which are described by the wave function ψ_n, the mean value of $< I_x + iI_y >$ over all the molecules in the sample will be

$$\overline{< I_x + iI_y >} = \sum_n p_n < I_x + iI_y >_n$$

$$= \sum_n p_n \sum_{j,k} C_{nk} C^*_{nj} (\phi^*_j | \underset{\sim}{I}^+ | \phi_k)$$

$$= \sum_{j,k} (\phi^*_j | \underset{\sim}{I}^+ | \phi_k) \sum_n p_n C_{nk} C^*_{nj} \qquad (6)$$

We now define two matrices. The first, I^+, has as the element at the intersection of row j and column k the element

$$I^+_{jk} = (\phi^*_j | \underset{\sim}{I}^+ | \phi_k) \qquad (7)$$

The second, which will be called the density patrix ρ, has

$$\rho_{kj} = \sum_n p_n C_{nk} C^*_{nj} \qquad (8)$$

Therefore (6) can be written

$$\overline{< I_x + iI_y >} = \sum_{j,k} I^+_{jk} \rho_{kj} = \mathrm{Tr}\ (I^+ \rho) \qquad (9)$$

where Tr (the trace) indicates the sum of the diagonal elements of the matrix $(I^+ \rho)$.

To get an idea of the physical significance of the terms in the density matrix ρ, note that although ρ has been derived with reference to the specific operator $\underset{\sim}{I}^+$, it is independent of this operator. In particular, when the operator $\underset{\sim}{I}^+$ is replaced by the unit operator $\underset{\sim}{1}$, the diagonal elements ρ_{kk} of ρ give the probability

of finding the entire sample in state ϕ_k. The diagonal elements can therefore be considered a measure of the relative population of the corresponding basis functions (i.e., of the "density" with which each basis function ϕ_k is populated). It is less simple to assign physical meaning to the off-diagonal elements. As a crude (and possibly misleading) approximation ρ_{kl} may be considered related to the number of molecules which are simultaneously in states ϕ_l and ϕ_k; that is, to the number capable of undergoing a transition between these two states.

These arguments may be clearer if the basis functions are chosen to be eigenfunctions of the Hamiltonian. Then the diagonal elements are the Boltzmann factors for each of the eigenfunctions, and as before, the off-diagonal elements are related to the possibility of transitions between the indicated states.

To return to the practical problem of calculating an AB-type spectrum, we see that the preceding discussion enables the problem to be reduced to that of calculating the elements of I^+ and of ρ, because the physical property measured by the spectrometer is equal to $N \langle \overline{I_x + iI_y} \rangle$ where N is the number of molecules in the sample and $\langle \overline{I_x + iI_y} \rangle$ is related to I^+ and ρ by (9). Calculation of the elements of $\underset{\sim}{I}^+$ is straightforward. For example (using the basis functions (2) and taking $\alpha^* = \alpha$ and $\beta^* = \beta$)

$$I^+_{11} = (\alpha(1)\alpha(2)|\underset{\sim}{I}^+|\alpha(1)\alpha(2)) = 0 \qquad (10a)$$

$$I^+_{12} = (\alpha(1)\alpha(2)|\underset{\sim}{I}^+|\alpha(1)\beta(2)) = 1 \qquad (10b)$$

etc.

and I^+ can immediately be written

$$I^+ = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{11}$$

Consequently

$$\mathrm{Tr} \begin{bmatrix} 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \rho_{11} & \rho_{12} & \rho_{13} & \rho_{14} \\ \rho_{21} & \rho_{22} & \rho_{23} & \rho_{24} \\ \rho_{31} & \rho_{32} & \rho_{33} & \rho_{34} \\ \rho_{41} & \rho_{42} & \rho_{43} & \rho_{44} \end{bmatrix}$$

$$= \rho_{21} + \rho_{31} + \rho_{42} + \rho_{43} \tag{12}$$

The problem of calculating the spectrum is now defined as that of calculating the four elements of ρ given in (12). We now proceed to this task. Our approach will begin with the equation analogous to the Schrödinger equation for the density matrix, first in the absence of exchange and relaxation phenomena. Then appropriate terms will be added to describe exchange and relaxation processes, and the resulting equation solved to yield expressions for the individual matrix elements of (12). The expression finally obtained will be a lineshape function for the general AB spectrum under conditions in which the A and B protons are exchanging with a rate constant comparable to their difference in chemical shift.

The nuclear spin wave functions Ψ_n obey the Schrödinger equation (13) in the absence of exchange and relaxation processes

$$\frac{d\Psi}{dt} = -i\hbar\underset{\sim}{\mathcal{H}}\Psi \tag{13}$$

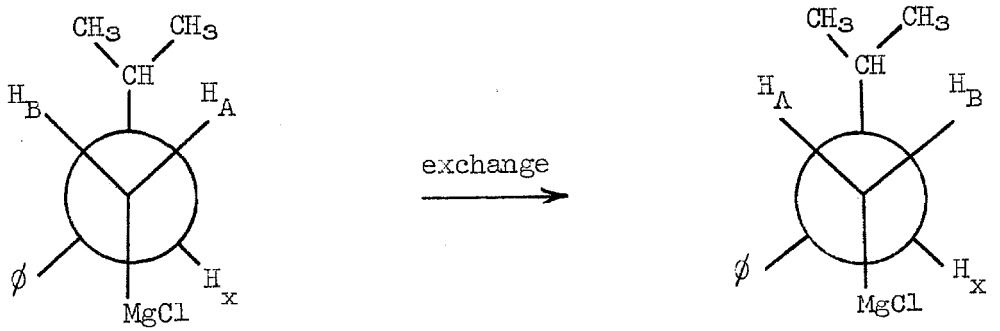
Here, $\underset{\sim}{\mathcal{H}}$ is the spin Hamiltonian determining the interaction of each nucleus with the applied fields and with the other nuclei. The corresponding equation for the density matrix can be shown to be (14) (48,49) when $\underset{\sim}{\mathcal{H}}$ has units of frequency, and frequencies are measured in radians/sec.

$$\frac{d\rho}{dt} = i[\rho\underset{\sim}{\mathcal{H}} - \underset{\sim}{\mathcal{H}}\rho] \qquad (14)$$

To describe the effect of exchange and relaxation processes on the density matrix, additional terms must be added to (14). The form of these exchange and relaxation terms will be discussed before considering the details of the Hamiltonian $\underset{\sim}{\mathcal{H}}$ appropriate to (14).

We will consider the form of the term describing exchange with reference to a specific AB-type Grignard reagent. For simplicity only the AB part of the spectrum will be considered. The complete ABX system will be treated later.

We schematically represent the exchange of the protons of the methylene group α to the magnesium atom by the reaction I → II.



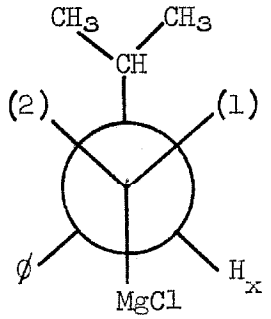
I II

The exchange process interchanges the two methylene protons H_A and H_B. If we say that H_A of I has spin α and H_B spin β before exchange, we

can write for the wave function of the AB system before exchange

$$\Psi_{before} = \alpha(1)\beta(2) \qquad (15)$$

where the indices 1 and 2 refer to the positions of the protons in the molecule.



This labeling of protons by their position is the most satisfactory method in a problem of this type, because any other method would suggest that nucleus A was somehow intrinsically different from nucleus B. The wave function for the same two protons after exchange is

$$\Psi_{after} = \alpha(2)\beta(1) \qquad (16)$$

The effect of the exchange on the spin wave function has thus been to interchange the indices of the two protons which exchanged. Kaplan (5) has defined an operator $\underset{\sim}{P}$, which interchanges the indices in the spin wave functions of protons which interchange in the molecule. In the case of the functions (2)

$$\underset{\sim}{P}(\alpha(1)\alpha(2)) = \alpha(2)\alpha(1) = \alpha(1)\alpha(2) \qquad (17a)$$

$$\underset{\sim}{P}(\alpha(1)\beta(2)) = \alpha(2)\beta(1) = \beta(1)\alpha(2) \qquad (17b)$$

$$\underset{\sim}{P}(\beta(1)\alpha(2)) = \beta(2)\alpha(1) = \alpha(1)\beta(2) \qquad (17c)$$

$$\underset{\sim}{P}(\beta(1)\beta(2)) = \beta(2)\beta(1) = \beta(1)\beta(2) \qquad (17d)$$

The operator $\underset{\sim}{P}$ takes ϕ_2 into ϕ_3, and ϕ_3 into ϕ_2, but does not change ϕ_1 and ϕ_4.

To write $\underset{\sim}{P}$ in the form of a matrix, one follows a simple procedure: operate on each function ϕ_j with $\underset{\sim}{P}$, and express the resulting wave function in terms of the original basis functions.

$$\underset{\sim}{P}\phi_1 = 1\phi_1 + 0\phi_2 + 0\phi_3 + 0\phi_4 \qquad (18a)$$

$$\underset{\sim}{P}\phi_2 = 0\phi_1 + 0\phi_2 + 1\phi_3 + 0\phi_4 \qquad (18b)$$

$$\underset{\sim}{P}\phi_3 = 0\phi_1 + 1\phi_2 + 0\phi_3 + 0\phi_4 \qquad (18c)$$

$$\underset{\sim}{P}\phi_4 = 0\phi_1 + 0\phi_2 + 0\phi_3 + 1\phi_4 \qquad (18d)$$

The array of coefficients on the right-hand side of (18) is the matrix of $\underset{\sim}{P}$. Here

$$P = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \qquad (19)$$

The operator $\underset{\sim}{P}$ describes the change in each of the basis functions associated with the AB system on interchanging the two protons. The corresponding change in the density matrix

$$P\rho P^{-1} = \rho' \qquad (20)$$

where ρ is the density matrix before exchange, ρ' is the corresponding density matrix after the exchange and P^{-1} is the inverse of P (in other words, $PP^{-1} = P^{-1}P = 1$). Here, ρ' is still defined with respect to the original basis set. We will not justify (20), but will merely point out that it is analogous to the similarity transformations commonly

used in molecular orbital theory (50). The operation P repeated twice returns the nuclei to their original positions. Hence

$$\underset{\sim}{P}\underset{\sim}{P} = 1 = \underset{\sim}{P}\underset{\sim}{P}^{-1} \tag{21}$$

which implies

$$\underset{\sim}{P} = \underset{\sim}{P}^{-1} \tag{22}$$

If τ is the lifetime of a proton in each site (the "pre-exchange" lifetime), the change in ρ due to exchange is

$$\left(\frac{d\rho}{dt}\right)_{\text{exchange}} = \frac{\rho_{\text{after exchange}} - \rho_{\text{before exchange}}}{\tau}$$

$$= \frac{P\rho P - \rho}{\tau} \tag{23}$$

For the AB spectrum under consideration, using (19)

$$P\rho P = \begin{bmatrix} \rho_{11} & \rho_{13} & \rho_{12} & \rho_{14} \\ \rho_{31} & \rho_{33} & \rho_{32} & \rho_{34} \\ \rho_{21} & \rho_{23} & \rho_{22} & \rho_{24} \\ \rho_{41} & \rho_{43} & \rho_{43} & \rho_{44} \end{bmatrix} \tag{24}$$

and

$$\left(\frac{d\rho}{dt}\right)_{\text{exchange}} = \frac{1}{\tau}\begin{bmatrix} 0 & \rho_{13}-\rho_{12} & \rho_{12}-\rho_{13} & 0 \\ \rho_{31}-\rho_{21} & \rho_{33}-\rho_{22} & \rho_{32}-\rho_{23} & \rho_{34}-\rho_{24} \\ \rho_{21}-\rho_{31} & \rho_{23}-\rho_{32} & \rho_{22}-\rho_{33} & \rho_{24}-\rho_{34} \\ 0 & \rho_{43}-\rho_{42} & \rho_{42}-\rho_{43} & 0 \end{bmatrix} \tag{25}$$

Our treatment of the corresponding term for the change in ρ due to relaxation will be very approximate. Previous discussion has suggested that the diagonal terms of ρ are related to the Boltzmann factors of the corresponding energy levels. The spin-lattice relaxation

time $1/T_1$ can be regarded as the rate constant for the restoration of thermal equilibrium among the populations of the energy levels following a perturbation.

Correspondingly, the spin-spin relaxation time $1/T_2$ is approximately the rate constant for the process restoring the normal induced magnetization in the x-y plane, after a perturbation. This normal value is of course zero. We have seen previously that the magnitude of the induced magnetization is determined by the off-diagonal elements of ρ. We therefore write

$$\left(\frac{d\rho}{dt}\right)_{\text{relaxation}} = \frac{1}{T_1}\,(\rho_o - \rho)_D + \frac{1}{T_2}\,(-\rho)_{OD} \qquad (26)$$

where the subscripts D and OD refer to diagonal and off-diagonal elements, respectively, and ρ_o is the value of ρ at thermal equilibrium.

Equation (26) applied to an AB system (or any other involving four basis functions) is

$$\left(\frac{d\rho}{dt}\right)_{\text{relaxation}} = \begin{bmatrix} 1/T_1(\rho_o-\rho)_{11} & -\rho_{12}/T_2 & -\rho_{13}/T_2 & -\rho_{14}/T_2 \\ -\rho_{21}/T_2 & 1/T_1(\rho_o-\rho)_{22} & -\rho_{23}/T_2 & -\rho_{24}/T_2 \\ -\rho_{31}/T_2 & -\rho_{32}/T_2 & 1/T_1(\rho_o-\rho)_{33} & -\rho_{34}/T_2 \\ -\rho_{41}/T_2 & -\rho_{42}/T_2 & -\rho_{43}/T_2 & 1/T_1(\rho_o-\rho)_{44} \end{bmatrix} \qquad (27)$$

Addition of (25) and (27) to (14) gives an equation (46) describing the motion of the density matrix under the influence of exchange and relaxation processes.

$$\frac{d\rho}{dt} = \left(\frac{d\rho}{dt}\right)_{\text{exchange}} + \left(\frac{d\rho}{dt}\right)_{\text{relaxation}} + i[\rho\mathcal{H} - \mathcal{H}\rho] \qquad (46)$$

In order to complete evaluation of (14), the form of the Hamiltonian must be known. We will use the Hamiltonian ordinarily employed in analysis of high resolution n.m.r. spectra, with an added term to take into account the effect of the rotating radio-frequency field. The nomenclature used will conform with that used in a recent text (51), except that all frequencies will have the units radians/sec.

In the stationary laboratory coordinate frame

$$\mathcal{H} = \mathcal{H}^{(0)} + \mathcal{H}^{(1)} + \mathcal{H}^{(t)} \tag{28}$$

where

$$\mathcal{H}^{(0)} = \sum_i H_o(1-\sigma(i))\gamma I_z(i) \tag{29}$$

gives the interaction of the nuclear magnetic moments with the applied external field H_o directed along the z axis of the coordinate system. Here, $\sigma(i)$ is the shielding constant for nucleus i, and γ is the gyromagnetic ratio;

$$\mathcal{H}^{(1)} = \sum_{i<j} J_{ij}\, \underset{\sim}{I}(i)\cdot\underset{\sim}{I}(j) \tag{30}$$

describes the spin-spin interaction between the nuclei (J_{ij} is the spin coupling constant between nuclei i and j) and determines the

$$\mathcal{H}^{(t)} = \sum_j \gamma H_1 (I_x(j)\sin\omega t + iI_y(j)\cos\omega t) \tag{31}$$

interaction between the nuclear magnetic moments and a magnetic field with amplitude H_1 rotating at frequency ω in the x-y plane.

In the usual technique of spin-spin analysis, $\mathcal{H}^{(t)}$ is neglected and $\mathcal{H}^{(0)} + \mathcal{H}^{(1)}$ alone are used to construct an energy

level diagram for the molecule being considered; here we want to include the driving term $\mathcal{H}^{(t)}$ explicitly. Rather than work in the stationary coordinate frame, in which $\mathcal{H}^{(t)}$ has a complex time dependence, it is convenient to transform these equations into a coordinate system rotating at the frequency ω of the H_1 field. It can be shown (52) that under these conditions the field $H_o(1-\sigma(i))$ is replaced by an "effective" field H_{er}

$$H_{er} = H_o(1-\sigma(i)) - \omega/\gamma \qquad (32)$$

In the rotating frame, $\mathcal{H}^{(0)}$ and $\mathcal{H}^{(t)}$ can be written

$$\mathcal{H}^{(0)} = \sum_i I_z(i)[\gamma H_o(1-\sigma(i)) - \omega] \qquad (33)$$

$$\mathcal{H}^{(t)} = \sum_i \gamma H_1 I_x(i) \qquad (34)$$

$\mathcal{H}^{(1)}$ is unchanged by the change in coordinates. The details of these transformations will not concern us here. It is however useful to point out that the physical significance of the change of coordinates is simply to eliminate the time dependence of H_1: in the rotating frame H_1 appears as a stationary vector directed along the x axis. In the laboratory frame, the nucleus precesses about the axis of the field $H_o(1-\sigma(i))$ with an angular frequency called the Larmor frequency

$$-\omega_o = \gamma H_o(1-\sigma(i)) \qquad (35)$$

In the rotating frame, the nucleus has a precession frequency equal to the difference between the Larmor frequency and the rotation frequency of the coordinate system.

Using the Hamiltonians (30) and (33), the matrix elements of $\mathcal{H}^{(0)} + \mathcal{H}^{(1)}$ can easily be evaluated for the AB problem. The terms $\mathcal{H}^{(0)} + \mathcal{H}^{(1)}$ and $\mathcal{H}^{(t)}$ are evaluated separately for convenience. For example

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{11} = (\alpha(1)\alpha(2)|\mathcal{H}^{(0)} + \mathcal{H}^{(1)}|\alpha(1)\alpha(2))$$

$$= \frac{\gamma H_o}{2}(2-\sigma(1) - \sigma(2)) - \omega + \frac{J}{4} \qquad (36a)$$

Similarly

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{22} = \frac{\gamma H_o}{2}(\sigma(1) - \sigma(2)) - \frac{J}{4} \qquad (36b)$$

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{33} = \frac{\gamma H_o}{2}(\sigma(2) - \sigma(1)) - \frac{J}{4} \qquad (36c)$$

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{44} = -\frac{\gamma H_o}{2}(2-\sigma(1) - \sigma(2)) + \omega - \frac{J}{4} \qquad (36d)$$

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{23} = [\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{32} = \frac{J}{2} \qquad (36e)$$

We define

$$\delta = \gamma H_o(\sigma(1) - \sigma(2)) \qquad (37a)$$

$$\Delta = \omega - \frac{\gamma H_o}{2}(2-\sigma(1) - \sigma(2)) \qquad (37b)$$

Equation (37b) has the effect of shifting the zero of frequency to a point midway between the resonance frequencies of H(1) and H(2).

Hence

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}] = \begin{bmatrix} -\Delta + J/4 & & & \\ & \delta - J/4 & J/2 & \\ & J/2 & -\delta - J/4 & \\ & & & \Delta - J/4 \end{bmatrix} \qquad (38)$$

and the matrix $[\rho(\mathcal{H}^{(0)} + \mathcal{H}^{(1)}) - (\mathcal{H}^{(0)} + \mathcal{H}^{(1)})\rho]$ follows immediately. This last matrix is quite lengthy, and will not be written in detail, because we will see later (see the discussion preceding (47)) that only four of its elements (the 21, 31, 42 and 43 elements) are pertinent to the problem. These elements are given in (39); here $[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{ij}$ means the element in row i and column j of the matrix $[\rho(\mathcal{H}^{(0)} + \mathcal{H}^{(1)}) - (\mathcal{H}^{(0)} + \mathcal{H}^{(1)})\rho]$.

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{21} = (-\Delta - \frac{\delta}{2} + \frac{J}{2})\rho_{21} + (-\frac{J}{2})\rho_{31} \qquad (39a)$$

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{31} = (-\Delta + \frac{\delta}{2} + \frac{J}{2})\rho_{31} + (-\frac{J}{2})\rho_{21} \qquad (39b)$$

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{42} = -(\Delta - \frac{\delta}{2} + \frac{J}{2})\rho_{42} + (\frac{J}{2})\rho_{43} \qquad (39c)$$

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{43} = -(\Delta + \frac{\delta}{2} + \frac{J}{2})\rho_{43} + (\frac{J}{2})\rho_{42} \qquad (39d)$$

To evaluate the elements of the commutator of ρ with $\mathcal{H}^{(t)}$ $[\rho\mathcal{H}^{(t)} - \mathcal{H}^{(t)}\rho]$ we follow an approximation procedure outlined by Alexander. The matrix of $\mathcal{H}^{(t)}$ is easily evaluated for the basis functions (2). For example, since $\underset{\sim}{I}_x(\alpha) = \beta/2$ and $\underset{\sim}{I}_x(\beta) = \alpha/2$

$$(\alpha(1)\alpha(\alpha)\left|\underset{\sim}{I}_x(1) + \underset{\sim}{I}_x(2)\right|\alpha(1)\alpha(2)) = 0 \qquad (40a)$$

$$(\alpha(1)\alpha(2)\left|\underset{\sim}{I}_x(1) + \underset{\sim}{I}_x(2)\right|\alpha(1)\beta(2)) = \frac{1}{2} \qquad (40b)$$

etc.

$$\mathcal{H}^{(t)} = \gamma H_1 \sum_i I_x(i) = \frac{\gamma H_1}{2}\begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \qquad (40c)$$

Alexander makes the reasonable approximation that $\mathcal{H}^{(t)}$ has a negligible effect on the diagonal terms of ρ, and that the diagonal terms of ρ are much larger than its off-diagonal terms. This approximation is legitimate because the radio-frequency field is very weak compared with the static field. Then, since the diagonal terms are the Boltzmann factors for the corresponding energy levels (see the discussion following (9))

$$\rho_{kk} = \frac{\exp(-\hbar/kT(\phi_k|\mathcal{H}^{(0)} + \mathcal{H}^{(1)}|\phi_k))}{\sum_j \exp(-\hbar/kT(\phi_k|\mathcal{H}^{(0)} + \mathcal{H}^{(1)}|\phi_k))} \qquad (41)$$

Expanding (41) to first order in the small number $(-\hbar/kT(\mathcal{H}^{(0)} + \mathcal{H}^{(1)}))$ and calling the denominator N

$$N\rho_{kk} = 1-\hbar/kT(\mathcal{H}^{(0)} + \mathcal{H}^{(1)}) \qquad (42a)$$

$$\simeq 1-\hbar/kT(\gamma H_o(F_z)_k) \qquad (42b)$$

The step from (42a) to (42b) is justified because the contribution of the shielding parameters $\sigma(i)$ and the coupling constants to the total energy is small compared with the energy of orienting the protons with or against the static field H_o. To these approximations, ρ for the AB case will be

$$\rho \simeq \frac{1}{N}\begin{bmatrix} 1-\hbar\gamma H_o/kT & & 0 \\ & 1 & \\ & & 1 \\ 0 & & 1+\hbar\gamma H_o/kT \end{bmatrix} \qquad (43)$$

and taking the commutator of (43) with (40c)

$$[\rho\mathcal{H}^{(t)} - \mathcal{H}^{(t)}\rho] = C \begin{bmatrix} 0 & -1 & -1 & 0 \\ 1 & 0 & 0 & -1 \\ 1 & 0 & 0 & -1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \qquad (44a)$$

where

$$C = \frac{\gamma^2 \hbar H_o H_1}{2NkT} \qquad (44b)$$

Alexander (48) has shown that in general

$$\langle \phi_k | \gamma H_1 (\rho \sum_i I_x(i) - \sum_i I_x(i)\rho) | \phi_j \rangle$$

$$= \mp 2C (\phi_k | \sum_i I_x(i) | \phi_j) \qquad (45)$$

when ϕ_k and ϕ_j differ in their value of F_z by ± 1, respectively, and is zero otherwise.

Before proceeding, let us briefly review what has been accomplished so far. The observed n.m.r. signal for an AB spectrum has been related to four elements of the spin density matrix by (12). The Schrödinger equation describing the behavior of the entire density matrix in the absence of exchange and relaxation effects has been evaluated in terms of a specific high-resolution Hamiltonian, and two terms have been added describing the effect of exchange and relaxation.

$$\frac{d\rho}{dt} = \left(\frac{d\rho}{dt}\right)_{exchange} + \left(\frac{d\rho}{dt}\right)_{relaxation} + i[\rho\mathcal{H} - \mathcal{H}\rho] \qquad (46)$$

We now wish to obtain explicit expressions for the four matrix elements of (46) (i.e. ρ_{21}, ρ_{31}, ρ_{42} and ρ_{43}) pertinent to the problem, in terms of J, δ, Δ and τ. To do so, we make the assumption that the spectrum is being observed under conditions of slow passage. In other words, the spectrum is being swept so slowly that the rate of change of the signal amplitude with time is very small. Under these conditions we can set (46) equal to zero. The resulting matrix equation can equally well be written as 16 linear algebraic equations (each equation being the sum of the ij th element from each of the matrices). If we select from these equations the ones which contain any of the four elements of ρ which are of interest, we obtain four simultaneous equations.

$$\frac{d\rho_{21}}{dt} = \frac{\rho_{31}-\rho_{21}}{\tau} - \frac{\rho_{21}}{T_2} + i\left(-\Delta - \frac{\delta}{2} + \frac{J}{2}\right)\rho_{21} + i\left(-\frac{J}{2}\right)\rho_{31} + iC = 0 \qquad (47a)$$

$$\frac{d\rho_{31}}{dt} = \frac{\rho_{21}-\rho_{31}}{\tau} - \frac{\rho_{31}}{T_2} + i\left(-\Delta + \frac{\delta}{2} + \frac{J}{2}\right)\rho_{31} + i\left(-\frac{J}{2}\right)\rho_{2} + iC = 0 \qquad (47b)$$

$$\frac{d\rho_{42}}{dt} = \frac{\rho_{43}-\rho_{42}}{\tau} - \frac{\rho_{42}}{T_2} - i\left(\Delta - \frac{\delta}{2} + \frac{J}{2}\right)\rho_{42} + i\left(\frac{J}{2}\right)\rho_{43} + iC = 0 \qquad (47c)$$

$$\frac{d\rho_{43}}{dt} = \frac{\rho_{42}-\rho_{43}}{\tau} - \frac{\rho_{43}}{T_2} - i\left(\Delta + \frac{\delta}{2} + \frac{J}{2}\right)\rho_{43} + i\left(\frac{J}{2}\right)\rho_{42} + iC = 0 \qquad (47d)$$

These may conveniently be solved by Cramer's rule. For example

$$\rho_{21} = \frac{\begin{vmatrix} -iC & \frac{1}{\tau} - i\frac{J}{2} \\ -iC & \left[-\frac{1}{\tau} - \frac{1}{T_2} - i\left(\Delta - \frac{\delta}{2} - \frac{J}{2}\right)\right] \end{vmatrix}}{\begin{vmatrix} \left[-\frac{1}{\tau} - \frac{1}{T_2} - i\left(\Delta + \frac{\delta}{2} - \frac{J}{2}\right)\right] & \frac{1}{\tau} - i\frac{J}{2} \\ \frac{1}{\tau} - i\frac{J}{2} & \left[-\frac{1}{\tau} - \frac{1}{T_2} - i\left(\Delta - \frac{\delta}{2} - \frac{J}{2}\right)\right] \end{vmatrix}} \qquad (48a)$$

$$\rho_{31} = \frac{\begin{vmatrix} \left[-\frac{1}{\tau} - \frac{1}{T_2} - i\left(\Delta + \frac{\delta}{2} - \frac{J}{2}\right)\right] & -iC \\ \frac{1}{\tau} - i\frac{J}{2} & -iC \end{vmatrix}}{\begin{vmatrix} \left[-\frac{1}{\tau} - \frac{1}{T_2} - i\left(\Delta + \frac{\delta}{2} - \frac{J}{2}\right)\right] & \frac{1}{\tau} - i\frac{J}{2} \\ \frac{1}{\tau} - i\frac{J}{2} & \left[-\frac{1}{\tau} - \frac{1}{T_2} - i\left(\Delta - \frac{\delta}{2} - \frac{J}{2}\right)\right] \end{vmatrix}} \qquad (48b)$$

The corresponding equations for ρ_{43} and ρ_{42} are the same as those for ρ_{21} and ρ_{31} respectively, except that the sign of J is changed.

To simplify the calculations, we make the assumption at this point that $1/T_2 = 0$; in other words, the assumption that the natural line widths are small when exchange is very fast or very slow.

The equations (48) are expanded and added and the numerator and denominator in each of the resulting expressions multiplied by the complex conjugate of its denominator, in order to put the expression into a form with a pure real denominator.

$$\frac{\rho_{21} + \rho_{31}}{C} = \frac{2\Delta^3 - 4J\Delta^2 + \Delta\left(2J^2 - \frac{\delta^2}{2} + \frac{8}{\tau^2}\right) + \frac{J\delta^2}{2} + i\left(\frac{\delta^2}{\tau}\right)}{\Delta^4 - 2J\Delta^3 + \Delta^2\left(\frac{4}{\tau^2} - \frac{\delta^2}{2} + J^2\right) + \Delta\delta^2\frac{J}{2} + \frac{\delta^4}{16}} \qquad (49a)$$

$$\frac{\rho_{42} + \rho_{43}}{C} = \frac{2\Delta^3 + 4J\Delta^2 + \Delta\left(2J^2 - \frac{\delta^2}{2} + \frac{8}{\tau^2}\right) - \frac{J\delta^2}{2} + i\left(\frac{\delta^2}{\tau}\right)}{\Delta^4 + 2J\Delta^3 + \Delta^2\left(\frac{4}{\tau^2} - \frac{\delta^2}{2} + J^2\right) - \Delta\delta^2\frac{J}{2} + \frac{\delta^4}{16}} \qquad (49b)$$

The sum of (49a) and (49b) defines the general line-shape function for an AB spectrum (with the natural line width $1/T_2 + 1/T_1$ set equal to zero) because Equation (12) indicates that at each frequency Δ in the spectrum the intensity of the signal is proportional to this sum (the constant of proportionality is of course C).

Before using this equation to calculate a representative AB-type spectrum, it is useful to examine the simpler case which results when J is set equal to zero, i.e., the case of two uncoupled protons exchanging between sites of different chemical shift. In this example, the imaginary part of the sum of (49a) and (49b) (the part describing the absorption signal) will be

$$\frac{\rho_{21} + \rho_{31} + \rho_{42} + \rho_{43}}{C} = \frac{\frac{2\delta^2}{\tau}}{\Delta^4 + \Delta^2 \left(\frac{4}{\tau^2} - \frac{\delta^2}{2}\right) + \frac{\delta^4}{16}} \qquad (50)$$

From (50) we can conveniently calculate the positions of the peak maxima by setting the derivative of the absorption signal with respect to frequency equal to zero

$$\frac{\partial}{\partial \Delta}\left(\frac{\rho_{21} + \rho_{31} + \rho_{42} + \rho_{43}}{C}\right) = \Delta^3 + \Delta\left(\frac{2}{\tau^2} - \frac{\delta^2}{4}\right) = 0 \qquad (51)$$

which has roots

$$\Delta = 0, \quad \Delta = \pm \frac{1}{2\tau}\sqrt{\tau^2\delta^2 - 8} \qquad (52)$$

The non-zero roots of (52) correspond to peak maxima in the region of pre-exchange lifetimes up to the point at which the peaks coalesce (at $\tau^2\delta^2 = 8$). The difference between these roots gives

the experimentally observed separation Δ_e between the peaks as a function of τ

$$\Delta_e = \frac{1}{\tau}\sqrt{\tau^2\delta^2 - 8} \qquad (53)$$

This equation is identical with that obtained by Gutowsky and Holm (44c) starting from the Bloch equations, when account is taken of the difference in the definition of τ in the two treatments (Gutowsky's τ is one-half that in (53)). Note that the units of δ in these equations are radians/sec. To apply (53) to measurements in units of cps., it must be written

$$\nu_e = \frac{1}{2\pi\tau}\sqrt{4\pi^2\nu^2\tau^2 - 8} \qquad (54)$$

where ν_e equals the observed separation in cps., and ν is the difference in chemical shift between the two kinds of proton in the extreme of slow exchange.

Two examples of the dependence of the appearance of an AB spectrum on the rate of interchange between the A and B protons are shown in Figures 13 and 14. The former is a plot of (50) when $J = \delta = 2$ rad./sec. To calculate the points for this curve, a value was obtained for the imaginary part of (49a)

$$\frac{\rho_{21} + \rho_{31}}{\delta^2 C} = \frac{\frac{1}{\tau}}{\Delta^4 - 2J\,\Delta^3 + \Delta^2\left(\frac{4}{\tau^2} - \frac{\delta^2}{2} + J^2\right) + \Delta\,\frac{\delta^2 J}{2} + \frac{\delta^4}{16}} \qquad (55a)$$

$$= \frac{\frac{1}{\tau}}{(\Delta^4 - 4\Delta^3 + 2\Delta^2 + 4\Delta + 1) + 4\Delta\,\frac{2}{\tau^2}} \qquad (55b)$$

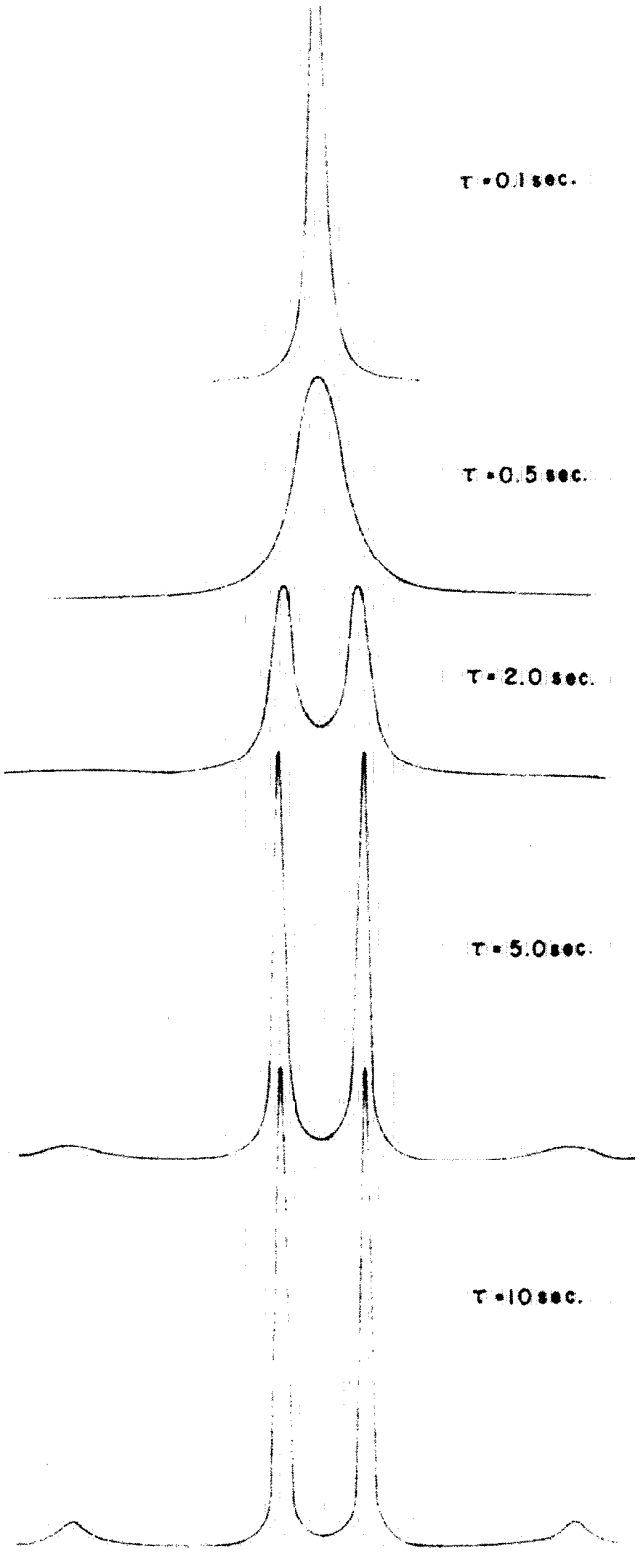


Fig. 13. Calculated line-shapes for an AB spectrum with $J = \delta = 2$ rad./sec., for different values of the pre-exchange lifetime τ.

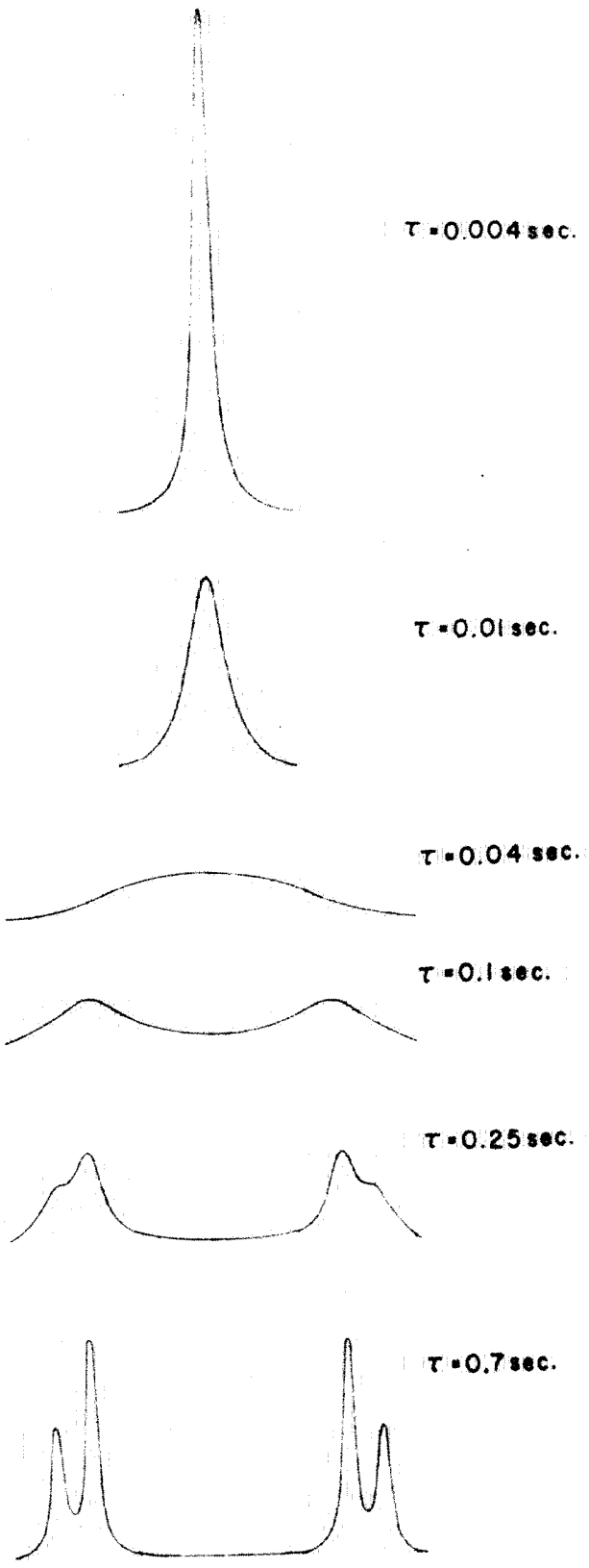


Fig. 14. Calculated line-shapes for an AB spectrum with $J = 1.18$ cps. and $\delta = 9.85$ cps., as a function of the pre-exchange lifetime τ. The separation between the outer lines of the slow exchange spectrum is 11.2 cps.

for values of Δ separated by 0.1 rad./sec., from $\Delta = 3.0$ to $\Delta = -1.0$, and the complete spectrum was then obtained by adding the curve so obtained to its mirror image around the point $\Delta = 0$. (The factor $\delta^2 C$ in the denominator of (55) is a scaling factor, and is important only when intensities from different calculations are to be compared.) This operation is legitimate because the value $\rho_{21} + \rho_{31}$ at each point Δ is easily seen to be identical with that of $\rho_{24} + \rho_{34}$ at $-\Delta$.

The values of J and δ chosen are not typical of most organic compounds. However, the same spectra will be obtained for values of J and δ larger than 2 by some factor, and for the corresponding values of τ divided by the same factor. For example, if the values $\Delta_N = a\Delta$, $J_N = aJ$, $\delta_N = a\delta$ and $\tau_N = \frac{\tau}{a}$ are substituted into (55a), one obtains

$$\frac{\rho_{21} + \rho_{31}}{C\delta^2_N/a^2} = \frac{(\frac{1}{a})\ (\frac{1}{\tau_N})}{(\frac{1}{a^4})(\Delta^4_N - 2J_N\Delta^3_N + \Delta^2_N(\frac{4}{\tau^2_N} - \frac{\delta^2_N}{2} + J^2_N) + \Delta_N \frac{\delta^2_N J_N}{2} + \frac{\delta^4_N}{16})} \qquad (56)$$

which will clearly have the same shape as (55a).

To use (55a) for measurements in units of cps., it is rewritten

$$\frac{\rho_{21} + \rho_{31}}{8\pi^2\delta^2 C} = \frac{\frac{1}{\tau}}{(\nu^4 - 2J\nu^3 + \nu^2\ (\frac{1}{(\pi\tau)^2} - \frac{\delta^2}{2} + J^2) + \nu\ \frac{\delta^2 J}{2} + \frac{\delta^4}{16})} \qquad (57)$$

Figure 14 shows spectra plotted for several values of τ using (57) when $J = 1.18$ cps., and $\delta = 9.85$ cps. (The reasons for choosing these values is that they are important in calculating the corresponding spectra for bis-(3,3-dimethylbutyl)-magnesium).

The contrast between the response to a change in exchange rate for these two types of AB spectra is instructive. In Figure 13 J/δ is relatively large. The low intensity outer lines broaden and for all practical purposes disappear before any major change occurs in the strong central lines. In Figure 14, J/δ is relatively small. Here, the two A components broaden and collapse before either shows an appreciable shift toward the B lines. Qualitatively it seems clear from (55a) that the lines of an AB spectrum which will show the effect of exchange most strikingly will be those with low intensities.

The purpose behind the derivation of (49) is to develop a method of obtaining activation parameters from the temperature dependence of complicated coupled spin systems. The most practical method of obtaining such information from (49) is presently unclear. It would be possible to differentiate the summed expression for $(\rho_{21} + \rho_{31} + \rho_{42} + \rho_{43})$ in a manner analogous to that used to obtain (52). The derivative obtained would be expected to be a seventh-degree equation, with its seven roots corresponding to the maxima and minima in the AB spectrum. Such an equation has not been obtained, because it would be impractically complicated for hand calculation.

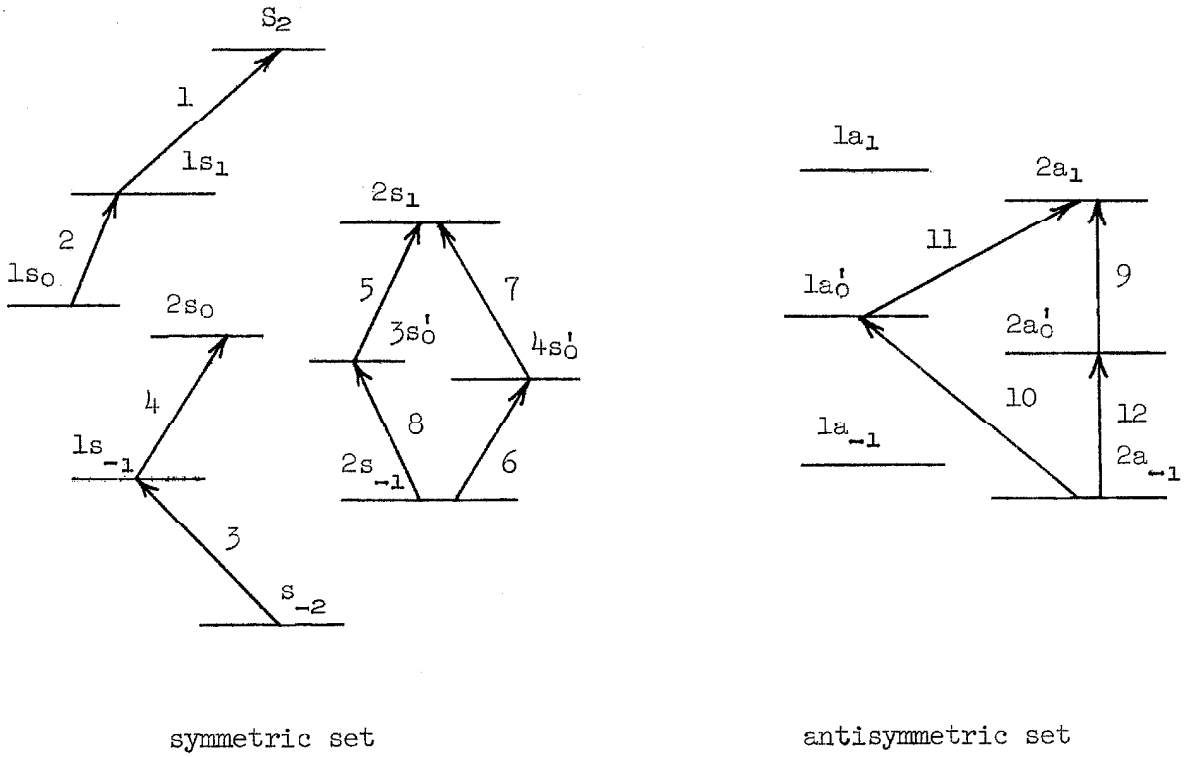
An alternative procedure would be to calculate the spectrum expected for different values of τ using the values of J and δ obtained from the slow-exchange spectrum, and compare these with the observed spectra. This procedure would also be quite tedious for hand calculation. Either method should, however, be readily amenable to machine calculation.

With this introduction to Alexander's procedure, we now turn to analogous calculations for the system of practical interest in this work: the AA'XX' spectrum of the 3,3-dimethylbutylmagnesium compounds. These calculations are very similar to those we have just completed and yield closely analogous results.

The schematic spectrum and energy-level diagram for the AA'XX' spectrum is given in Figure 15. (The actual values of the corresponding energy levels for bis-(3,3-dimethylbutyl)-magnesium obtained by machine computation are given in the experimental section.) The symmetric and antisymmetric sets are separated for clarity. Transitions for the A protons are numbered to correspond to the schematic spectrum below.

The exchange process which determines the appearance of the spectrum of these organometallics is an interchange of the two α protons. The effect of this exchange is to average the two vicinal coupling constants J and J' (53). In the slow-exchange limit, $L = J + J'$ will be different from zero (in the particular case of bis-(3,3-dimethylbutyl)-magnesium in diethyl ether solution at room temperature L = 9.8 cps.); in the fast-exchange limit L will be zero. Examination of the energies of an AA'XX' spectrum reveals that only the $3s'_o$, $4s'_o$, $1a'_o$ and $2a'_o$ levels depend on L.

These are given in Table VI.



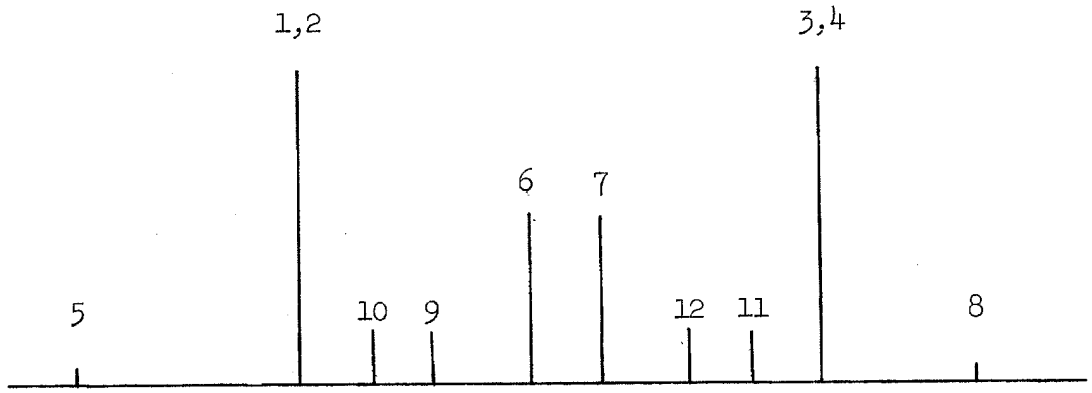


Fig. 15. Schematic energy-level diagram and transition assignments for bis-(3,3-dimethylbutyl)-magnesium.

Table VI

Selected Stationary-State Wave Functions and Energies of an AA'XX' System

State	Energy
$3s_o'$	$-\frac{1}{2}K - \frac{1}{2}(K^2 + L^2)^{1/2}$
$4s_o'$	$-\frac{1}{2}K + \frac{1}{2}(K^2 + L^2)^{1/2}$
$1a_o'$	$-\frac{1}{2}K + \frac{1}{2}(M^2 + L^2)^{1/2}$
$2a_o'$	$-\frac{1}{2}K - \frac{1}{2}(M^2 + L^2)^{1/2}$

Here,

$$K = J_A + J_B \qquad L = J - J'$$
$$M = J_A - J_B \qquad N = J + J'$$

Rapid exchange would therefore be predicted to average transitions between symmetric states with $F_z = 1$ and the $3s_o'$ and $4s_o'$ states, and correspondingly between antisymmetric states with $F_z = 1$ and the $1a_o'$ and $2a_o'$ states.

Our approach to this problem will be to treat the symmetric and antisymmetric quartets separately, and sum then to obtain the total spectrum due to the 5, 10, 9, 6, 7, 12, 11 and 8 transitions. Since the 1,2 and 3,4 transitions are not appreciably affected by the exchange process, we will not deal with them explicitly.

We choose as the basis set for the quartet of antisymmetric transitions the correctly antisymmetrized combinations of basic product functions (58). The 1 and 2 protons are the protons which exchange.

$$\phi_1 = \frac{1}{\sqrt{2}}\alpha(1)\alpha(2)(\alpha(3)\beta(4) - \beta(3)\alpha(4)) \qquad 2a_1 \qquad (58a)$$

$$\phi_2 = \frac{1}{2}(\alpha(1)\beta(2) + \beta(1)\alpha(2))\ (\alpha(3)\beta(4) - \beta(3)\alpha(4)) \qquad 2a_0 \qquad (58b)$$

$$\phi_3 = \frac{1}{2}(\alpha(1)\beta(2) - \beta(1)\alpha(2))\ (\alpha(3)\beta(4) - \beta(3)\alpha(4)) \qquad 2a_0 \qquad (58c)$$

$$\phi_4 = \frac{1}{\sqrt{2}}\beta(1)\beta(2)(\alpha(3)\beta(4) - \beta(3)\alpha(4)) \qquad 2a_{-1} \qquad (58d)$$

The first problem is to determine which elements of ρ determine the shape of this portion of the spectrum. The matrix of $\underset{\sim}{I}^+$ is determined as before (10) (11); i.e.,

$$\left(\frac{1}{\sqrt{2}}\alpha\alpha(\alpha\beta - \beta\alpha)\middle|\underset{\sim}{I}^+\middle|\frac{1}{2}(\alpha\beta + \beta\alpha)\ (\alpha\beta - \beta\alpha)\right) = \frac{1}{\sqrt{2}} \qquad (59a)$$

$$\left(\frac{1}{\sqrt{2}}\alpha\alpha(\alpha\beta - \beta\alpha)\middle|\underset{\sim}{I}^+\middle|\frac{1}{2}(\alpha\beta - \beta\alpha)\ (\alpha\beta + \beta\alpha)\right) = 0 \qquad (59b)$$

etc.

and

$$I^+ = \begin{bmatrix} 0 & \frac{1}{\sqrt{2}} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\sqrt{2}} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \qquad (59c)$$

Therefore, the equation analogous to (12) is

$$\mathrm{Tr}(I^+\rho) = \frac{1}{\sqrt{2}}(\rho_{21} + \rho_{42}) \qquad (60)$$

This equation indicates that ρ_{21} and ρ_{42} are sufficient to describe the entire spectrum. The spectrum of the antisymmetric quartet will be described by the two elements of ρ in (60). To derive expressions for these terms, we must again obtain expressions

for the exchange matrix PρP and the commutator of ρ with the Hamiltonian $[\rho\mathcal{H} - \mathcal{H}\rho]$.

The operator $\underset{\sim}{P}$ exchanges the two nuclei in the 1 and 2 positions. Operating with $\underset{\sim}{P}$ on each of the basis functions (58) in turn we obtain

$$\underset{\sim}{P}\phi_1 = 1\phi_1 + 0\phi_2 + 0\phi_3 + 0\phi_4 \tag{61a}$$

$$\underset{\sim}{P}\phi_2 = 0\phi_1 + 1\phi_2 + 0\phi_3 + 0\phi_4 \tag{61b}$$

$$\underset{\sim}{P}\phi_3 = 0\phi_1 + 0\phi_2 - 1\phi_3 + 0\phi_4 \tag{61c}$$

$$\underset{\sim}{P}\phi_4 = 0\phi_1 + 0\phi_2 + 0\phi_3 + 1\phi_4 \tag{61d}$$

The matrix of P analogous to (19) is therefore

$$P = \begin{bmatrix} 1 & & & 0 \\ & 1 & & \\ & & -1 & \\ 0 & & & 1 \end{bmatrix} \tag{62}$$

and the counterpart of (24)

$$P\rho P = \begin{bmatrix} \rho_{11} & \rho_{12} & -\rho_{13} & \rho_{14} \\ \rho_{21} & \rho_{22} & -\rho_{23} & \rho_{24} \\ -\rho_{31} & -\rho_{32} & \rho_{33} & -\rho_{34} \\ \rho_{41} & \rho_{42} & -\rho_{43} & \rho_{44} \end{bmatrix} \tag{63a}$$

$$\frac{P\rho P - \rho}{\tau} = \frac{1}{\tau}\begin{bmatrix} 0 & 0 & -2\rho_{13} & 0 \\ 0 & 0 & -2\rho_{23} & 0 \\ -2\rho_{31} & -2\rho_{32} & 0 & -2\rho_{34} \\ 0 & 0 & -2\rho_{43} & 0 \end{bmatrix} \tag{63b}$$

The equation (27) describing the relaxation processes would be identical for this problem and the AB problem. We will neglect it altogether in this problem: that is, we assume that the natural linewidth in the absence of exchange is zero.

We use the same Hamiltonian (equations (28), (30), (33) and (34)) for this problem as for the AB problem. However by noting that the Hamiltonian $\mathcal{H}^{(0)} + \mathcal{H}^{(1)}$ (i.e. (30) plus (33)) has exactly the same form as that used by Pople, Schneider and Bernstein (54) with the addition of a term $\sum_i - I_z(i)\omega$, we may save considerable effort by using their matrix elements for the AA'XX' system. (The difference in the units of the two Hamiltonians, cps. versus radians/sec., should be kept in mind.) Thus, the matrix elements of (30) and (33) for an $F_z = 0$ state will be identical with those of Pople (54); the diagonal matrix elements for $F_z = \pm 1$ states will be the corresponding elements of Pople's with a term $\mp \omega$ added; $F_z = \pm 2$ states would have $\mp 2\omega$ added etc. We can then write analogously to (38),

$$\mathcal{H}^{(0)}+\mathcal{H}^{(1)} = \begin{bmatrix} \nu_A - \frac{1}{4}K + \frac{1}{2}M - \omega & & & \\ & -\frac{1}{4}K + \frac{1}{2}M & & \\ & & -\frac{1}{4}K - \frac{1}{2}M & \\ & & & -\nu_A - \frac{1}{4}K + \frac{1}{2}M + \omega \end{bmatrix} \tag{64}$$

We are interested in all the elements of $[\rho(\mathcal{H}^{(0)}+\mathcal{H}^{(1)}) - (\mathcal{H}^{(0)}+\mathcal{H}^{(1)})\rho]$ which contain ρ_{21} or ρ_{24} (60). These are given below: (here, we have defined $\Delta = \nu_A - \omega$ and the notation is the same as in (29)).

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{21} = \rho_{21}(\Delta) + \rho_{31}\left(\frac{L}{2}\right) \tag{65a}$$

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{31} = \rho_{31}(\Delta+M) + \rho_{21}\left(\frac{L}{2}\right) \tag{65b}$$

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{42} = \rho_{42}(\Delta) + \rho_{43}\left(-\frac{L}{2}\right) \tag{65c}$$

$$[\rho,\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{43} = \rho_{43}(\Delta-M) + \rho_{42}\left(-\frac{L}{2}\right) \tag{65d}$$

The elements of $[\rho\mathcal{H}^{(t)} - \mathcal{H}^{(t)}\rho]$ are obtained from (45) to yield an equation analogous to (44a)

$$[\rho\mathcal{H}^{(t)} - \mathcal{H}^{(t)}\rho] = \frac{C}{\sqrt{2}}\begin{bmatrix} 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \tag{66}$$

Inserting (66), (65) and (63) into (46) and again making the assumption that the experiment is being carried out under slow-passage conditions, we obtain as before four linear algebraic equations in ρ_{21}, ρ_{31}, ρ_{42} and ρ_{43}

$$\frac{d\rho_{21}}{dt} = i\rho_{21}(\Delta) + i\rho_{31}\left(\frac{L}{2}\right) + \frac{iC}{\sqrt{2}} = 0 \tag{67a}$$

$$\frac{d\rho_{31}}{dt} = -\frac{2\rho_{31}}{\tau} + i\rho_{31}(\Delta+M) + i\rho_{21}\left(\frac{L}{2}\right) = 0 \tag{67b}$$

$$\frac{d\rho_{42}}{dt} = i\rho_{42}(\Delta) + i\rho_{43}\left(-\frac{L}{2}\right) + \frac{iC}{\sqrt{2}} = 0 \tag{67c}$$

$$\frac{d\rho_{43}}{dt} = -\frac{2\rho_{43}}{\tau} + i\rho_{43}(\Delta-M) + \rho_{42}\left(-\frac{L}{2}\right) = 0 \tag{67d}$$

We need solve these only for ρ_{21} and ρ_{42}

$$\rho_{21} = \frac{\begin{vmatrix} -iC/\sqrt{2} & i\,L/2 \\ 0 & -\frac{2}{\tau} + i(\Delta+M) \end{vmatrix}}{\begin{vmatrix} i\Delta & i\,L/2 \\ i\,L/2 & -\frac{2}{\tau} + i(\Delta+M) \end{vmatrix}} \qquad (68a)$$

$$\rho_{42} = \frac{\begin{vmatrix} -iC/\sqrt{2} & -i\,L/2 \\ 0 & -\frac{2}{\tau} + i(\Delta-M) \end{vmatrix}}{\begin{vmatrix} i\Delta & -i\,L/2 \\ -i\,L/2 & -\frac{2}{\tau} + i(\Delta-M) \end{vmatrix}} \qquad (68b)$$

These equations are expanded in the same manner as the corresponding equations (48) to yield

$$\frac{\sqrt{2}\,\rho_{21}}{C} = \frac{-2\Delta^3 - 4M\Delta^2 + \Delta\left(\frac{L^2}{2} - 2M^2 - \frac{8}{\tau^2}\right) + \frac{L^2M}{2} + i\left(\frac{L^2}{\tau}\right)}{\Delta^4 + 2M\Delta^3 + \Delta^2\left(M^2 - \frac{L^2}{2} + \frac{4}{\tau^2}\right) + \Delta\left(-\frac{L^2M}{2}\right) + \frac{L^4}{16}} \qquad (69a)$$

$$\frac{\sqrt{2}\,\rho_{42}}{C} = \frac{-2\Delta^3 + 4M\Delta^2 + \Delta\left(\frac{L^2}{2} - 2M^2 - \frac{8}{\tau^2}\right) - \frac{L^2M}{2} + i\left(\frac{L^2}{\tau}\right)}{\Delta^4 - 2M\Delta^3 + \Delta^2\left(M^2 - \frac{L^2}{2} + \frac{4}{\tau^2}\right) + \Delta\left(\frac{L^2M}{2}\right) + \frac{L^4}{16}} \qquad (69b)$$

The sum of these two equations is the line-shape function for the asymmetric quartet of an AA'XX' spectrum, under the assumption that the natural line width of the lines in the absence of exchange is zero. The parallel between these equations and those derived previously (49) for an AB-type spectrum is very close. If one makes the substitutions $L = \delta$, $M = J$ and $\Delta = -\Delta$ in (69), the equations obtained are identical with (49) (the substitution $\Delta = -\Delta$ reflects the fact that the direction of increasing Δ was defined differently in the derivation of (49) and (69)).

The imaginary part of (69) describes the absorption signal from the asymmetric quartet (lines 10, 9, 12 and 11). The spectrum of the symmetric quartet (lines 5, 6, 7 and 8) can be obtained by a precisely analogous procedure. If one uses the basis set

$$\phi_1 = \alpha(1)\alpha(2)\,\frac{1}{\sqrt{2}}\,[\alpha(3)\beta(4) + \beta(3)\alpha(4)] \qquad (70a)$$

$$\phi_2 = \frac{1}{2}\,[\alpha(1)\beta(\alpha) + \beta(1)\alpha(2)]\,[\alpha(3)\beta(4) + \beta(3)\alpha(4)] \qquad (70b)$$

$$\phi_3 = \frac{1}{2}\,[\alpha(1)\beta(2) - \beta(1)\alpha(2)]\,[\alpha(3)\beta(4) - \beta(3)\alpha(4)] \qquad (70c)$$

$$\phi_4 = \beta(1)\beta(2)\,\frac{1}{\sqrt{2}}\,[\alpha(3)\beta(4) + \beta(3)\alpha(4)] \qquad (70d)$$

where the 1 and 2 protons are geminal to the magnesium atom, and the matrix elements of $\mathcal{H}^{(0)} + \mathcal{H}^{(1)}$ given in Pople (54), one obtains a sequence of equations identical with those obtained in the derivation of (69), except that K is substituted for M in each equation. The calculations will not be given in detail; the final line-shape equations are (71).

$$\frac{\sqrt{2}\,\rho_{21}}{C} = \frac{-2\Delta^3 - 4K\Delta^2 + \Delta\left(\frac{L^2}{2} - 2K^2 - \frac{8}{\tau^2}\right) + \frac{L^2K}{2} + i\left(\frac{L^2}{\tau}\right)}{\Delta^4 + 2K\Delta^3 + \Delta^2\left(K^2 - \frac{L^2}{2} + \frac{4}{\tau^2}\right) + \Delta\left(-\frac{L^2K}{2}\right) + \frac{L^4}{16}} \qquad (71a)$$

$$\frac{\sqrt{2}\,\rho_{42}}{C} = \frac{-2\Delta^3 + 4K\Delta^2 + \Delta\left(\frac{L^2}{2} - 2K^2 - \frac{8}{\tau^2}\right) - \frac{L^2K}{2} + i\left(\frac{L^2}{\tau}\right)}{\Delta^4 - 2K\Delta^3 + \Delta^2\left(K^2 - \frac{L^2}{2} + \frac{4}{\tau^2}\right) + \Delta\left(\frac{L^2K}{2}\right) + \frac{L^4}{16}} \qquad (71b)$$

The line-shape function for the combined 5, 10, 9, 6, 7, 12, 11 and 8 transitions of the A part of the AA'XX' spectrum is given by

the superposition of (69) and (71). This function has been evaluated for several values of τ; the resulting spectra are shown in Figure 16. These spectra were obtained by evaluating (69) and (71) separately for each value of τ, and superimposing the two resulting quartets. The weak 5 and 8 transitions were not included in the calculations. The actual functions evaluated in making these plots (i.e. (69) and (71) with the constants evaluated) are for (69).

$$\rho_{21}^{M} \alpha \frac{\frac{1}{\tau}}{\Lambda^4 + 2.36\ \Lambda^3 - 47.12\ \Delta^2 - 57.24\ \Lambda + 588.31 + \Delta^2/9.87\ \tau^2}$$

and for (71)

$$\rho_{21}^{K} \alpha \frac{\frac{1}{\tau}}{\Delta^4 + 61.56\ \Delta^3 + 898.90\ \Delta^2 - 1493.14\ \Delta + 588.31 + \Delta^2/9.87\ \tau^2}$$

The total intensity of absorption at each frequency Δ is proportional to $\rho_{21}^{M}(\Delta) + \rho_{21}^{M}(-\Delta) + \rho_{21}^{K}(\Delta) + \rho_{21}^{K}(-\Delta)$ where $\rho_{21}^{M}(\Delta)$ is the magnitude of ρ_{21}^{M} at Δ, and $\rho_{21}^{M}(-\Delta)$ is the corresponding value at $-\Delta$.

The assumption was made in these calculations that the spectrum of the 6 and 7 transitions would not change for values of τ greater than 0.0397 sec. The actual shapes calculated for these transitions for large τ are not appreciably shifted from their positions at τ = 0.0397 sec.; they are however much narrower. The line width actually calculated from (69) and (71) is of course misleading, because of the assumptions concerning the natural line widths. The effect of freezing the line-shape at the chosen value of τ is simply to approximate, in the simplest possible fashion, the slow-exchange line-shapes actually observed.

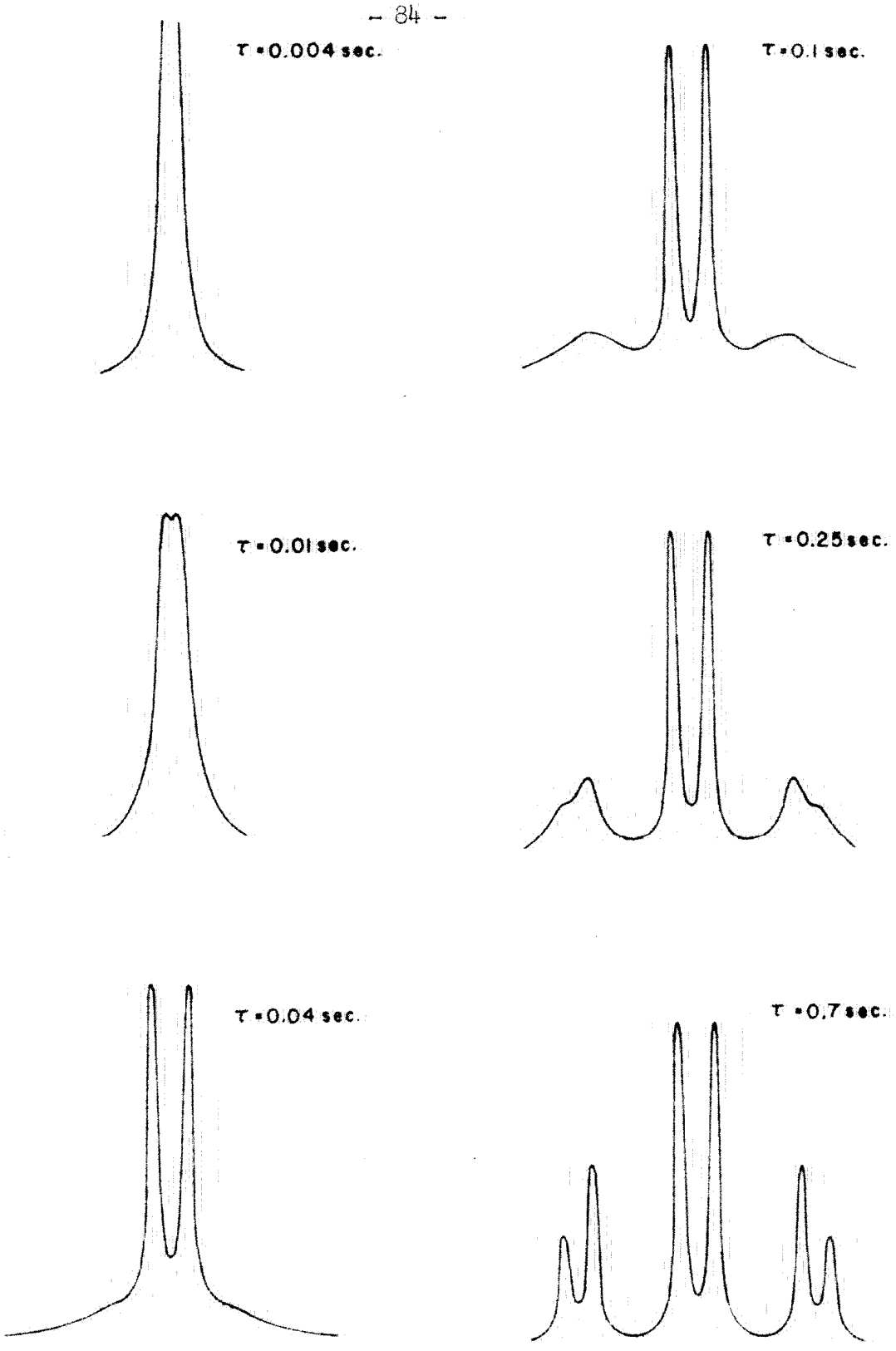


Fig. 16. Calculated line-shapes for the six central lines of the AA'XX' spectrum of the 3,3-dimethylbutylmagnesium compounds, at different values of the pre-exchange lifetime τ.

Qualitatively, one feature of the spectra calculated by this method is of particular interest: the antisymmetric transitions broaden and coalesce appreciably before the two symmetric transitions. This difference in sensitivity to the rate of exchange is clearly evident in the experimental spectra: the two center lines of the symmetric quartet coalesce at an appreciably higher temperature than do the transitions belonging to the antisymmetric quartet.

This difference in response to temperature provides another confirmation that exchange rather than change in conformational populations is reponsible for the observed simplification of the spectra at high temperatures. Figure 17 reproduces the spectra that would have been expected on the basis of major changes in conformational populations. These spectra were calculated on the assumption that a decrease in the larger vicinal coupling constant, due to a change in conformational populations, would be accompanied by an equal increase in the smaller vicinal coupling constant. This assumption is probably not strictly valid, but is sufficiently accurate for our qualitative purposes.

As the value of L is decreased in these spectra, the corresponding decrease in the separation between the 6 and 7 transitions is approximately proportional to the decrease in the separation between the 9,10 and 11,12 transitions: in other words, corresponding separations between transitions within the symmetric and antisymmetric quartets would be equally responsive to changes in conformer populations. This conclusion seems particularly reasonable if (following comparison of (69) and (71) with (49)) the transitions under discus-

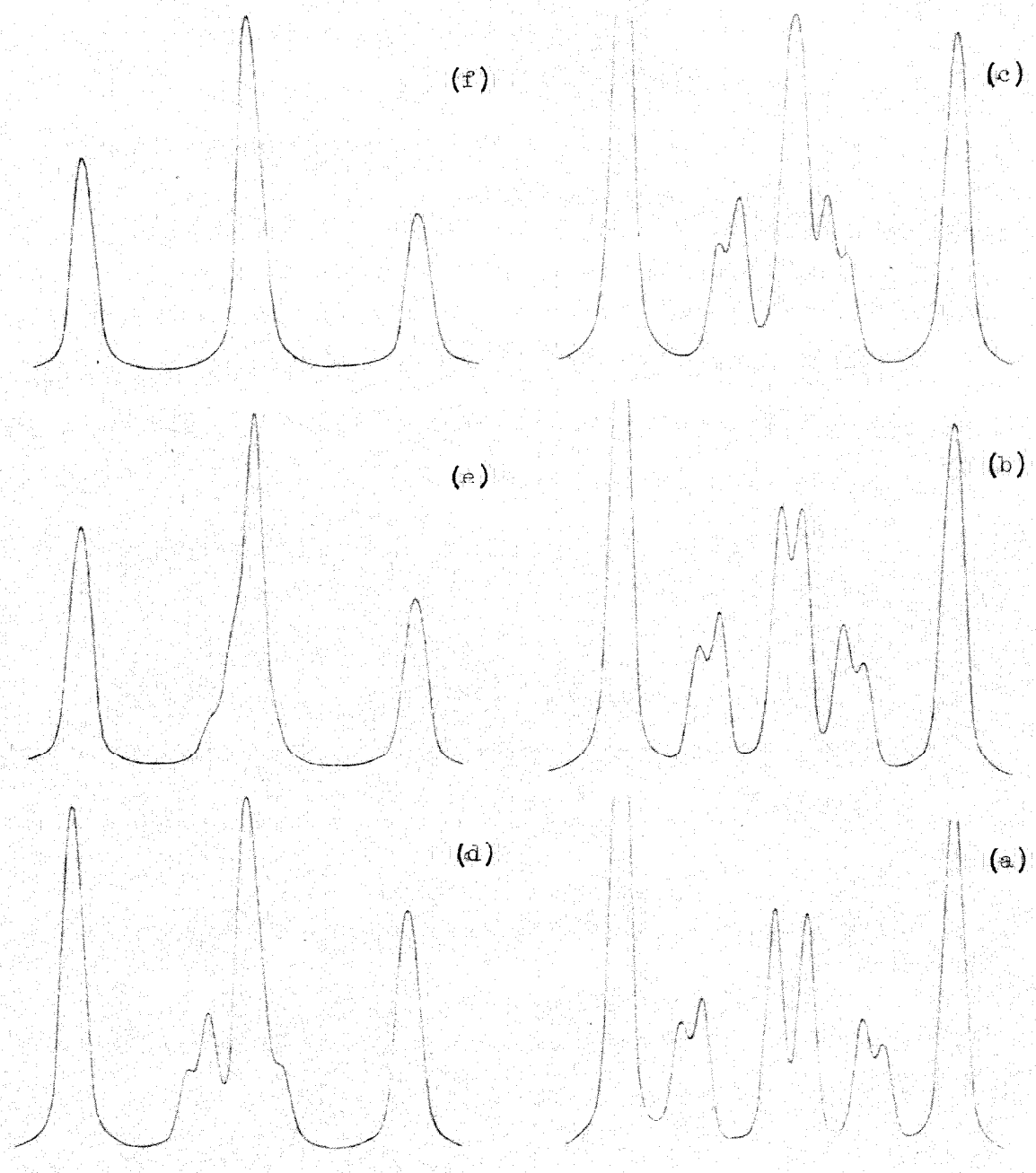


Fig. 17. Calculated spectra for an AA'XX' spectrum as a function of the difference between the vicinal coupling constants J and J' (in cps.): (a) J - J' = 9.85; (b) J - J' = 7.85; (c) J - J' = 5.85; (d) J - J' = 3.85; (e) J - J' = 1.85; (f) J - J' = 0.00. For all spectra, J_A = -15.98, J_B = -14.80 and J + J' = 18.17.

sion are considered as the superposition of two AB quartets, each having an effective chemical shift of L. As L is decreased, the changes in the two quartets would be expected to be roughly parallel.

Moreover, the spectra of Figure 17 indicate that no line-broadening effects would be expected, were changes in conformations responsible for the simplification of the spectra. For example, the separation between the 9 and 10 transitions remains clearly visible until these lines merge with the 6,7 transitions in the calculated spectra. By contrast, the separation between the 9 and 10 transitions in the observed spectra is lost in the broadening of these lines appreciably before the lines collapse. This behavior is in agreement with the spectra calculated on the basis of (69) and (71).

Qualitatively the spectra calculated from Alexander's treatment of exchange broadening confirm that exchange rather than population change is primarily responsible for the simplification of the experimental spectra at high temperatures. The problem of obtaining quantitative values for the activation parameters for the exchange process is not so straightforward.

The procedure adopted here was an approximate one, primarily because the quality of the spectra is generally not such that detailed comparison of calculated and observed spectra would be profitable. The 9 and 10, and 11 and 12 transitions respectively were each considered as one line (i.e., M was considered to be small compared with L) and (69) was treated as outlined earlier for an AX spectrum with J = 0 (equations (50) - (54)) to yield an approximate formula

relating the experimental separation ν_e between the 9,10 and 11,12 transitions at each temperature to the pre-exchange lifetime τ

$$\nu_e = \frac{1}{2\pi\tau}\sqrt{4\pi^2L^2\tau^2 - 8} \qquad (72a)$$

$$\frac{1}{\tau} = \pi\sqrt{(L^2-\nu_e^2)/2} \qquad (72b)$$

where ν_e and L are in cps. units. Activation parameters for the exchange process are obtained from the temperature dependence of $1/\tau$ by the familiar treatment based on the Arrhenius equation

$$\frac{1}{\tau} = k \qquad (73a)$$

$$k = Ae^{-E_a/RT} \qquad (73b)$$

where k is the rate constant for the exchange process, E_a is the activation energy for this process, and A is the pre-exponential term.

In principle, a plot of $\log(1/\tau)$ (obtained from (72b)) *versus* $1/T$ should be a straight line whose slope is E_a and whose intercept at some temperature is A. Figure 18 shows plots of $\log(1/\tau)$ *versus* $1/T$ for bis-(3,3-dimethylbutyl)-magnesium and 3,3-dimethylbutylmagnesium chloride in diethyl ether solution. The data on which these plots are based are given in the experimental section. Note, however, that the value of L used in these calculations is that observed at -65° (L = 10.5 cps.).

The most striking feature of these plots is their non-linearity. An explanation is suggested below for this behavior, and estimates of the activation energy for inversion obtained despite the curvature. It should however be emphasized that the error in the values of E_a

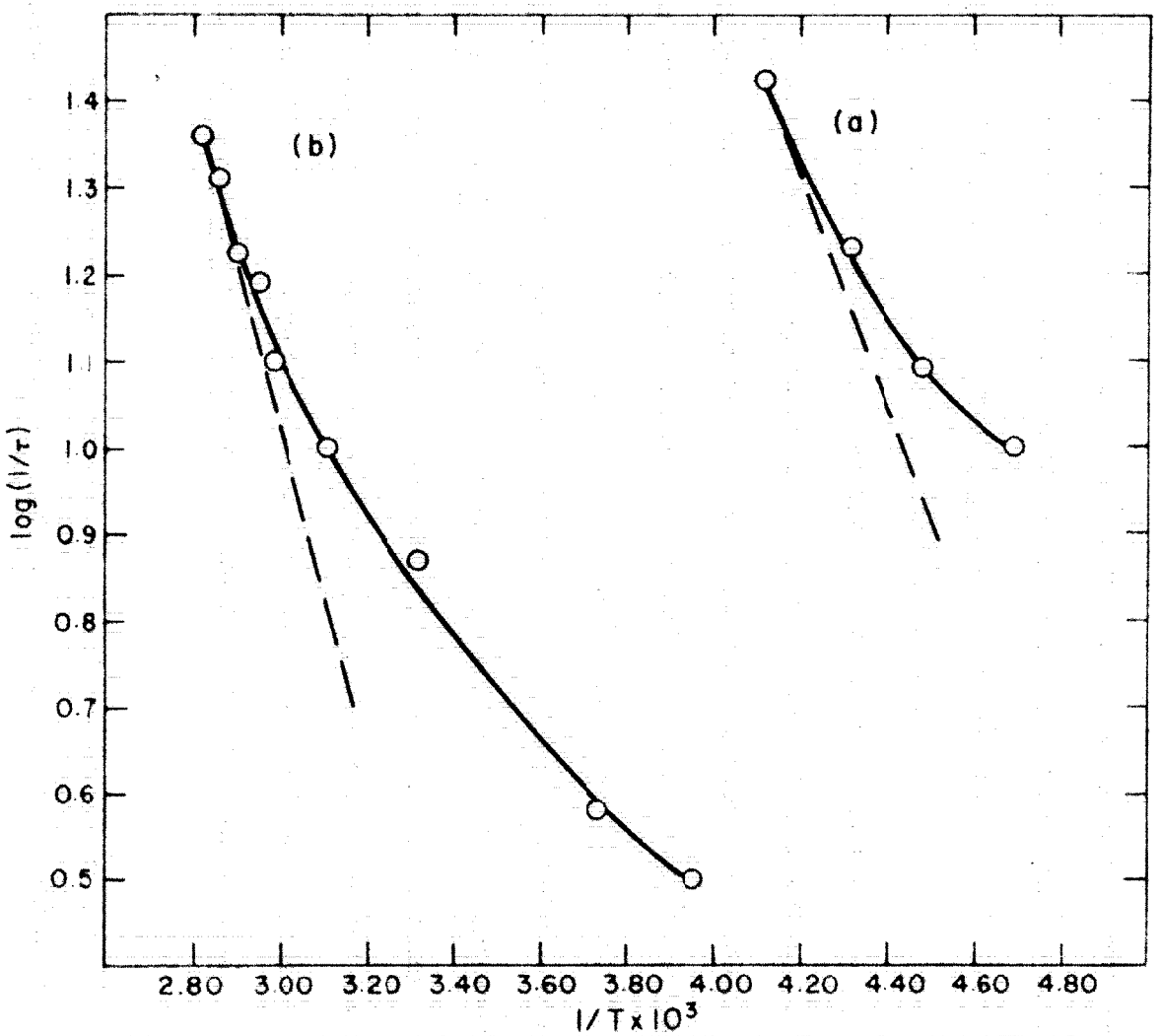


Fig. 18. Plot of $\log(1/\tau)$ as a function of $1/T$ for 3,3-dimethylbutylmagnesium chloride (a), and bis-(3,3-dimethylbutyl)-magnesium (b).

obtained from analysis of these spectra is large. Both large uncertainties in the original measurements of line separations (due both to the broadening of the peaks in the region of intermediate exchange and to effects of overlap with the other lines in the spectrum) and neglect of significant factors (e.g., $1/T_2$ and M) in the derivation of (72) combine to make kinetic analysis in this system very uncertain.

We suggest that the curvature in the plot of $\log(1/\tau)$ versus $1/T$ for 3,3-dimethylbutylmagnesium chloride and bis-(3,3-dimethylbutyl)-magnesium is a reflection of the fact that two different processes are averaging the vicinal coupling constants. One process (occurring to a significant extent only for $1/T \times 10^3 \tilde{<} 3.2$) has a relatively high temperature dependence and correspondingly high E_a; this process is most probably the inversion at the α carbon atom. It is proposed that the relatively temperature-insensitive averaging of coupling constants observed at low temperatures (i.e., $1/T \times 10^3$ between 4.0 and 3.4) is the consequence of small changes in the relative populations of the gauche and trans conformations of the organometallic compound.

Previously, the insensitivity of the separation between the strong 1,2 and 3,4 transitions in these spectra had been cited as evidence that major changes in conformational populations were not responsible for the changes observed in the spectrum. This argument is not inconsistent with the suggestion that relatively small changes in conformational populations are responsible for measurable changes in the separation of the 9 and 11 transitions. This latter separation is primarily determined by $L = J - J'$ (in the absence of exchange,

the separation between the 9 and 11 transitions is $[(J_A - J_B)^2 + (J - J')^2]^{1/2}$; $J_A - J_B$ is small and is not expected to vary appreciably with temperature). The separation between the 1,2 and 3,4 transitions is exactly $N = J + J'$. As the temperature of the sample is increased from its low temperature limit, the population of the gauche conformation of the organometallic compound will increase. Consequently, the larger of the two observed vicinal coupling constants will decrease and the smaller will increase toward their averaged high temperature value. These changes will partially cancel in the sum of the coupling constants N; they will be additive in the difference L.

Approximate calculations discussed previously suggested that a change of approximately 2 cps. would be observed in N if changes in conformer populations only were responsible for the observed changes in the spectra. The corresponding change in L would be approximately 8.5 cps. Hence, L would be expected to change approximately four times as rapidly as N as the conformer populations change. The separation of the 9 and 11 transitions changes by approximately 0.7 cps. from -65° to +28°. If this change were due entirely to changes in conformational populations, the corresponding change in the separation of the 1,2 and 3,4 transitions would be approximately 0.2 cps. This value is sufficiently close to experimental error in these spectra to be unobservable.

Experimental support for this explanation is provided by the low-temperature spectra of bis-(3,3-dimethylbutyl)-magnesium. Over the temperature range -65° to +29°, the measured separation

between the 9,10 and 11,12 transitions (this separation being approximately equal to L) decreases from 10.5 to 9.8 cps. The 9 and 10 transitions, and the 11 and 12 transitions remain clearly separated, and no broadening is apparent in any of the lines in the spectrum. Only at temperatures above approximately 49° do these transitions broaden and collapse following the pattern of the spectra calculated using Alexander's method. These observations support the thesis that the difference in energy between gauche and trans conformers is sufficiently small that a change in temperature from -65° to +30° results in an appreciable increase in the population of the higher energy (presumably gauche) conformer and a consequent decrease in L. The exchange process involving inversion of configuration only becomes important at temperatures above +50°.

If a temperature-dependent equilibrium between trans and gauche conformations is responsible for the low-temperature curvature in the plot of $\log(1/\tau)$ versus $1/T$, it should be possible to obtain approximate values for the activation parameters for the inversion process from the limiting high-temperature tangent to the plot. The slope of the tangent to the bis-(3,3-dimethylbutyl)-magnesium plot yields an activation energy of E_a = 8.6 kcal./mole; its intercept at $1/T = 2.86 \times 10^3$ yields a value for the pre-exponential factor of 10^7 sec.$^{-1}$. The corresponding values for 3,3-dimethylbutylmagnesium chloride are more uncertain, because the curve contains fewer points; the values obtained from the tangent to the curve at $1/T = 4.1 \times 10^3$ are E_a = 5.9 kcal./mole and $A = 10^7$ sec.$^{-1}$.

The significance of these numbers will be discussed along with those for 2-phenyl-3-methylbutylmagnesium chloride.

The temperature dependence of the α-proton spectrum of 2-phenyl-3-methylbutylmagnesium chloride depends on the response of the ABX spectrum to the exchange rate of a process interchanging the A and B protons. The AB part of the spectrum consists of two overlapping quartets. Figure 19 indicates the transitions which are expected to collapse under the influence of an exchange process averaging states 3' and 4', and 5' and 6'. We will outline a demonstration that each of these quartets behaves as an AB quartet with apparent chemical shifts as $\nu_B-\nu_A - J_{BX} - J_{AX}$ or $\nu_B-\nu_A - J_{BX} + J_{AX}$. The details of the calculations are formally identical with those for the AB spectrum discussed previously, and will not be reproduced.

We choose as the basis set for one quartet the four basic product functions:

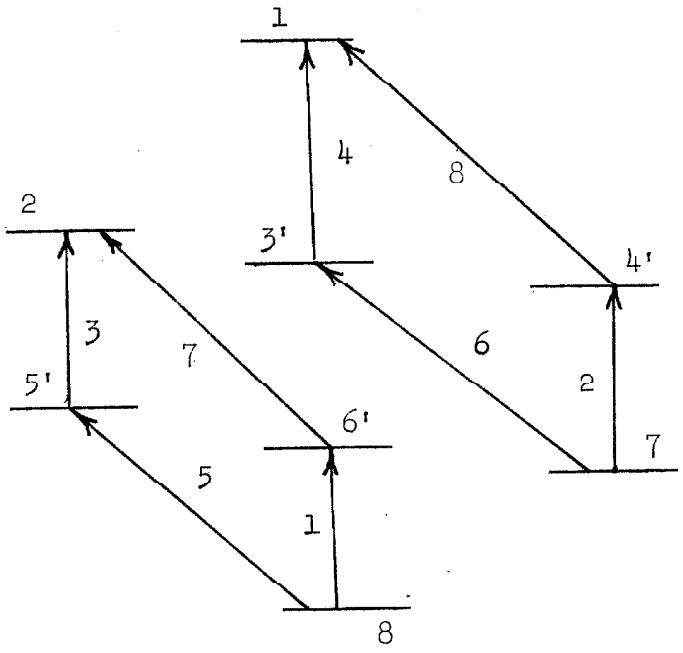
$$\phi_1 = \alpha(1)\alpha(2)\alpha(3) \qquad (74a)$$

$$\phi_2 = \alpha(1)\beta(2)\alpha(3) \qquad (74b)$$

$$\phi_3 = \beta(1)\alpha(2)\alpha(3) \qquad (74c)$$

$$\phi_4 = \beta(1)\beta(2)\alpha(3) \qquad (74d)$$

where the indices 1 and 2 refer to the protons α to the magnesium, and 3 refers to the X proton. The exchange operator P interchanges the indices 1 and 2 and has the form (75) identical with (19)



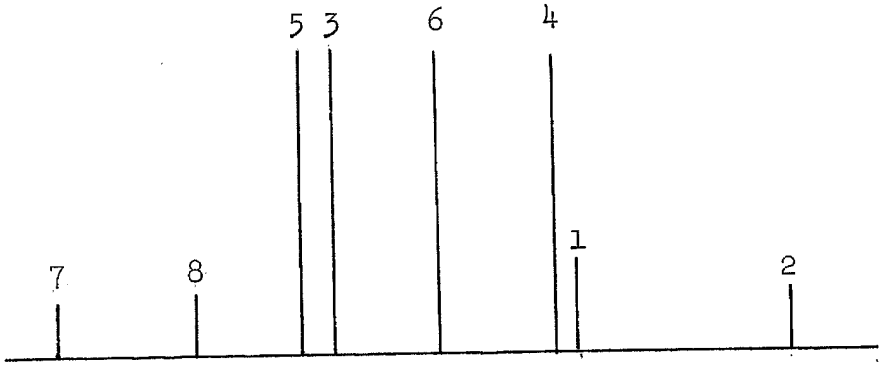


Fig. 19. Schematic energy-level diagram and spectrum for the AB part of an ABX spectrum. Transitions 1,2, 3 and 4 are A transitions; 5,6,7 and 8 are B transitions.

$$P = \begin{bmatrix} 1 & & & \\ & 0 & 1 & \\ & 1 & 0 & \\ & & & 1 \end{bmatrix} \qquad (75)$$

Because the matrix of $\underset{\sim}{I}^{+}$ for this problem is identical with (11), we can write immediately

$$\mathrm{Tr}(I^{+}\rho) = \rho_{21} + \rho_{31} + \rho_{42} + \rho_{43} \qquad (76)$$

The non-zero elements of $(\mathcal{H}^{(0)} + \mathcal{H}^{(1)})$ analogous to (36) can be obtained from Pople (55), using the method outlined previously to obtain (64).

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{11} = \tfrac{1}{2}(\nu(1) + \nu(2) + \nu(3)) + \tfrac{1}{4}(J_{12} + J_{23} + J_{31}) - \tfrac{3}{2}\omega \qquad (77a)$$

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{22} = \tfrac{1}{2}(\nu(1) - \nu(2) + \nu(3)) + \tfrac{1}{4}(-J_{12} - J_{23} + J_{31}) - \tfrac{1}{2}\omega \qquad (77b)$$

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{33} = \tfrac{1}{2}(-\nu(1) + \nu(2) + \nu(3)) + \tfrac{1}{4}(-J_{12} + J_{23} - J_{31}) - \tfrac{1}{2}\omega \qquad (77c)$$

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{44} = \tfrac{1}{2}(-\nu(1) - \nu(2) + \nu(3)) + \tfrac{1}{4}(J_{12} - J_{23} - J_{31}) - \tfrac{3}{2}\omega \qquad (77d)$$

$$[\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{23} = [\mathcal{H}^{(0)} + \mathcal{H}^{(1)}]_{32} = \tfrac{1}{2} J_{12} \qquad (77e)$$

Making the definitions

$$\Delta = \omega - \frac{\nu(2) + \nu(1)}{2} - \frac{J_{23} + J_{13}}{2} \qquad (78a)$$

$$\delta = \nu(2) - \nu(1) + J_{23} - J_{13} \qquad (78b)$$

we write for the matrix elements of $[\rho, \mathcal{H}^{(0)} + \mathcal{H}^{(1)}]$ containing ρ_{21}, ρ_{31}, ρ_{42} or ρ_{43} four equations identical with (29).

$$[\rho,\mathcal{H}^{(0)}+\mathcal{H}^{(1)}]_{21} = (-\Delta - \frac{\delta}{2} + \frac{J_{12}}{2})\rho_{21} + (-\frac{J_{12}}{2})\rho_{31} \qquad (79a)$$

$$[\rho,\mathcal{H}^{(0)}+\mathcal{H}^{(1)}]_{31} = (-\Delta + \frac{\delta}{2} + \frac{J_{12}}{2})\rho_{31} + (-\frac{J_{12}}{2})\rho_{21} \qquad (79b)$$

$$[\rho,\mathcal{H}^{(0)}+\mathcal{H}^{(1)}]_{42} = -(\Delta - \frac{\delta}{2} + \frac{J_{12}}{2})\rho_{42} + (\frac{J_{12}}{2})\rho_{43} \qquad (79c)$$

$$[\rho,\mathcal{H}^{(0)}+\mathcal{H}^{(1)}]_{43} = -(\Delta + \frac{\delta}{2} + \frac{J_{12}}{2})\rho_{43} + (\frac{J_{12}}{2})\rho_{42} \qquad (79d)$$

Finally the appropriate elements of (44) can be used without change in this problem.

It is therefore clear that this problem is formally identical with the AB problem, and that the solution of (46) for the elements of ρ in (76) will be identical with (49) with J_{12} substituted for J.

The analogous demonstration for the second quartet uses the basis set

$$\phi_1 = \alpha(1)\alpha(2)\beta(3) \qquad (80a)$$

$$\phi_2 = \alpha(1)\beta(2)\beta(3) \qquad (80b)$$

$$\phi_3 = \beta(1)\alpha(2)\beta(3) \qquad (80c)$$

$$\phi_4 = \beta(1)\beta(2)\beta(3) \qquad (80d)$$

and again has a solution of the form (49), with $J = J_{12}$ and $\delta = \nu(2) - \nu(1) - J_{23} + J_{13}$.

Analysis of the temperature dependence of the α-proton spectrum of 2-phenyl-3-methylbutylmagnesium chloride is complicated by the fact that only the four intense central lines of the AB part of the ABX spectrum can be observed, in the region of intermediate exchange rate.

Careful analysis of the temperature dependence of these spectra would involve, for example, comparing the observed separation between the 6 and 4 transitions at each temperature with spectra calculated using (49) with $\delta = \nu(2)-\nu(1) - J_{23} + J_{13}$, for several values of $1/\tau$, in order to obtain the dependence of $1/\tau$ on temperature. A plot of $\log(1/\tau)$ versus $1/T$ would then yield E_a and A in the manner outlined previously (73).

As an approximate alternative method for the calculation of activation parameters from the collapse of these spectra, we have calculated approximate "apparent" chemical shifts from the spectra at each temperature in the region of intermediate exchange rate and applied the formulas developed previously (54) for an AX system with J = 0 to these parameters to obtain the pre-exchange lifetimes. To calculate the apparent chemical shifts, the assumption was made that the positions of the weak outer lines could be approximated by adding or subtracting J_{12} from the appropriate inner lines. Values of $\nu_1-\nu_2$ could then be calculated from the resulting spectra by standard methods.

This procedure has several defects. The most serious of these is that the spectra calculated previously using typical AB parameters indicate clearly that the separation between the two A transitions is not exactly J_{AB} in the region of intermediate exchange: the weak outer line broadens and collapses toward the center more rapidly than the strong inner line. The only justification for using the procedure outlined above in this case is that the intensity of

the weak outer line is much less than that of the inner line, and that a fairly large error in determining its line position introduces only a small error in the value of $\nu_A - \nu_A$.

The values of $\nu_A - \nu_B$ obtained using this approximation were actually used directly in the Gutowsky and Holm procedure (44c). Activation energies and pre-exponential factors were obtained from the plots of $\log(1/\tau)$ versus $1/T$ shown in Figure 20. For 2-phenyl-3-methylbutylmagnesium chloride in diethyl ether the values obtained were E_a = 6.8 kcal./mole and A = 10^6 sec.$^{-1}$; for 2-phenyl-3-methylbutylmagnesium chloride in tetrahydrofuran the corresponding values were E_a = 17 kcal./mole and A = 10^{11} sec.$^{-1}$.

Of these two, the values in diethyl ether solution are probably the more accurate. The line separations in these spectra could be measured with higher accuracy than those in tetrahydrofuran by using the high-field ^{13}C ether satellite as an internal standard. The line separations in tetrahydrofuran solution were measured using a precalibrated sweep rate, and averaging upfield and downfield sweeps to decrease the error introduced by transient drifts in the field sweep. (Note that this method of obtaining line separations is less objectionable when applied to data to be used in the Gutowsky and Holm treatment than in other treatments, because the quantities used in determining E_a by this method are unitless.) However, regardless of the relative uncertainties in the sweep calibration, both the error in estimating the peak positions in the broad spectra of these organometallics, and the errors introduced by the assumptions made in calculating the chemical shifts, are sufficient to make the activation parameters obtained rather uncertain.

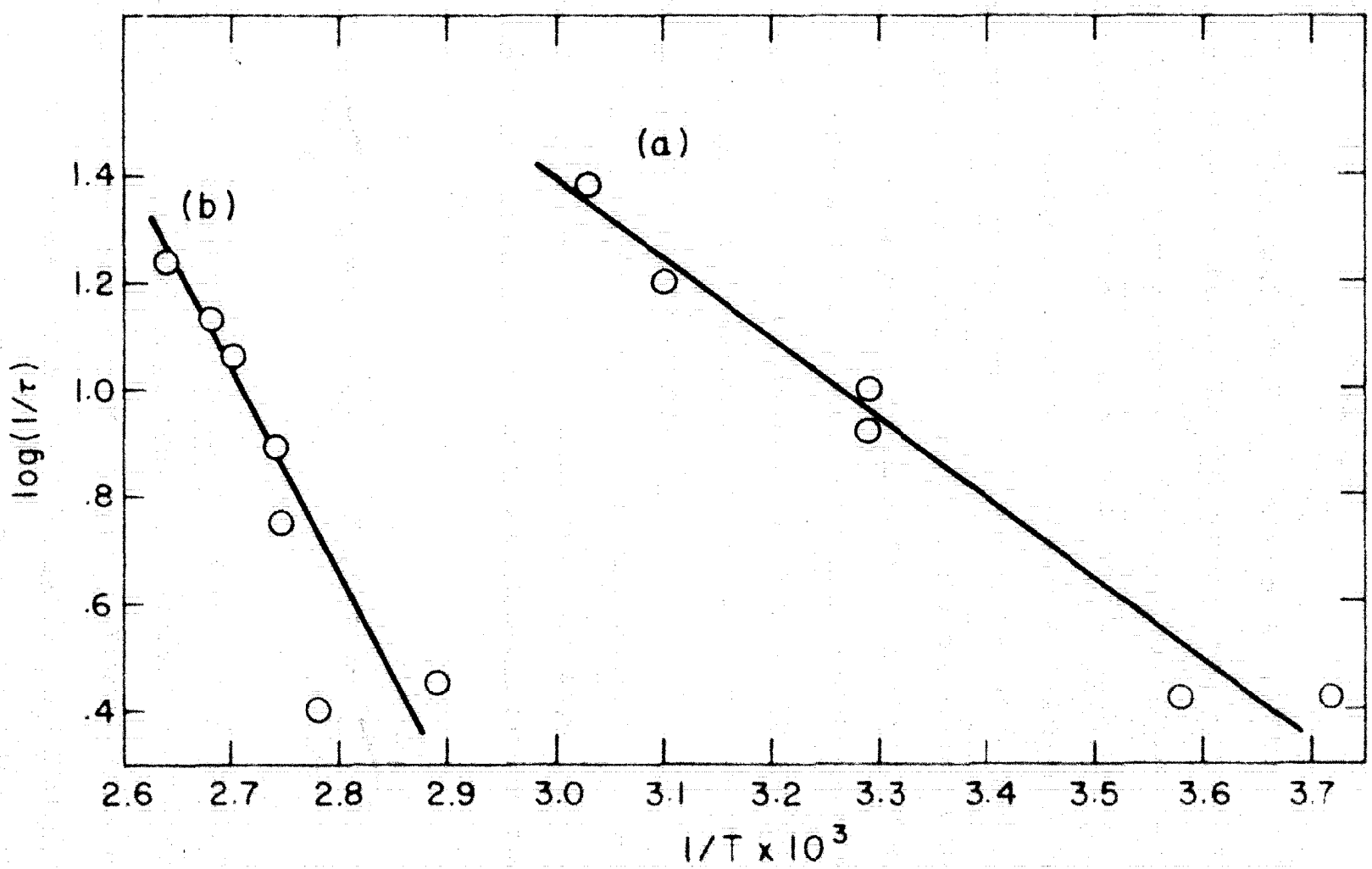
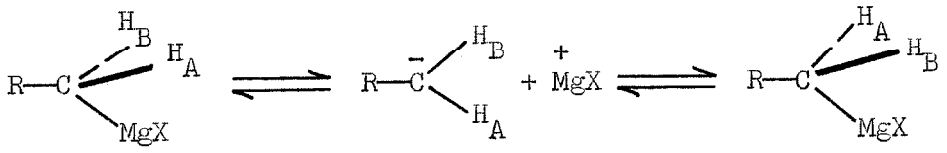


Fig. 20. Plot of $\log(1/\tau)$ as a function of $1/T$ for 2-phenyl-3-methylbutylmagnesium chloride: (a) tetrahydrofuran solution; (b) diethyl ether solution.

DISCUSSION

The experimental observations presented above indicate that inversion of configuration at the metal-bearing carbon atom of several typical primary Grignard reagents occurs with a rate constant in the range 1 $sec.^{-1}$ to 100 $sec.^{-1}$ at room temperature. It would be of considerable interest to reach some conclusion concerning the mechanism of the inversion from these data; unfortunately, those data presently available are insufficient to allow a firm decision to be made concerning any of the possible mechanisms for the inversion. Undeterred, in this section we will speculate briefly on the significance of these observations with regard to questions concerning the structure of the Grignard reagent and the mechanism of inversion of configuration at the carbon atom bonded to the magnesium.

The most important question to be asked concerning the mechanism of the inversion reaction concerns its kinetic order. If inversion proceeds by an uncomplicated ionization-recombination pathway, the inversion rate should be



approximately independent of the concentration of organometallic compound or magnesium salts in solution. If inversion is a bimolecular process, its rate should vary with the concentration of the reactants.

It is observed experimentally that the inversion rate does depend in a very striking manner on the concentration of the Grignard

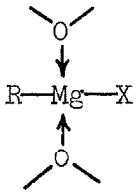
reagent in solution, being slower in dilute than in concentrated solution. The actual rate decrease accompanying a decrease in concentration can be estimated for 3,3-dimethylbutylmagnesium chloride from Figure 6 and Figure 18. The former indicates that a change in the concentration of the organometallic compound from approximately 15% to approximately 1% at -6° is sufficient to change the spectrum from its fast exchange form to its slow exchange form. The latter suggests that the fast exchange and slow exchange forms of the Grignard reagent spectra correspond to inversion rates differing by approximately a factor of 50.

This observed dependence of inversion rate on the concentration of Grignard reagent is in reasonable agreement with that which might be predicted using a bimolecular mechanism as the basis for prediction. Unfortunately, the observed change in inversion rate is also within the range which would be predicted on the basis of a unimolecular mechanism, provided the transition state for the inversion in the mechanism has appreciably more charge separation than the ground state. In this case, the change in rate would be a consequence of the change in the bulk dielectric constant of the solvent, accompanying the change in Grignard reagent concentration.

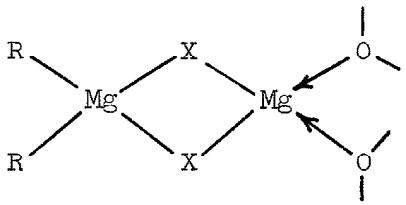
The effect of the concentration and kind of halogen anion present in solution is best discussed by considering the influence the anion might have on the transition state for the mono- and bimolecular reactions.

In a monomolecular ionization-recombination reaction, the anion would probably exert its influence by its effect on the carbon-

metal bond strength. The two most probable structures for an alkyl Grignard reagent in solution have been discussed in the introduction and are indicated here as I and II



I



II

Both have halogen anion bonded directly to the magnesium atom. A carbon-magnesium bond is a fairly covalent bond; increasing its covalent character should increase its strength. We suggest that the carbon-magnesium bond will be more covalent and consequently stronger for X = Cl than for X = Br. Following a suggestion of Bent (56), we reason that an increase in the electronegativity of a substituent X bonded to magnesium will increase the p character of the magnesium bonding orbital directed toward X. An increase in the p character of the Mg-X bond will be accompanied by a decrease in the p character of the magnesium bonding orbital directed toward carbon, or equivalently, an increase in the s character of this orbital. This increase in s character should shorten the C-Mg bond and increase the electron density in the region of the metal atom; that is, increase its covalent character and its strength. The order of carbon-metal bond strengths and covalent characters for these organomagnesium compounds would thus be predicted to be R-MgCl > R-MgBr > R-MgI > R-MgR. On the assumption that the ground-state bond strength is the most important factor in

determining the rate of inversion, we would predict that the rate of inversion should increase in the order R-MgR > R-MgI > R-MgBr > R-MgCl. In fact, the opposite order is observed.

If the mechanism of inversion if bimolecular, it probably involves electrophilic attack on the Grignard reagent by some species containing the fragment -MgX: either RMgX, MgX_2 or some more complicated magnesium containing species. The rate of inversion would then be expected to increase with increasing electrophilicity of the attacking species. The more electronegative the halogen atom attached to the magnesium, the more electrophilic the -MgX fragment should be. Hence, using a bimolecular model for the reaction and assuming that the rate depends primarily on the electrophilicity of the fragment -MgX, we predict that the rate of inversion should increase in the order R-MgCl > R-MgBr > R-MgI > R-MgR. This order is the one observed.

One important result should however be emphasized here which suggests that the anion present in solution <u>does</u> influence the inversion reaction in some manner other than through its effect on electrophilicity or on the bulk dielectric constant of the solution. Magnesium bromide added to a solution of 3,3-dimethylbutylmagnesium chloride in ether <u>slows</u> the rate of inversion. It would be inconsistent to assume that electrophilicity of the -MgX fragment were the sole important factor in determining the rate of inversion, and then to say that adding a weak electrophile to a strong electrophile should decrease the overall electrophilicity of the -MgX fragments in solution.

The spectrum observed for the mixture of Grignard reagent and magnesium bromide does not consist of two superimposed spectra corre-

sponding to "RMgCl" and "RMgBr" but rather of an averaged spectrum intermediate between the two. This observation suggests that migration of halide ion (or magnesium halide) between organometallic centers occurs rapidly in solution. In consequence, the solution of "RMgCl" with added magnesium bromide probably contains an equilibrium concentration of "RMgBr." We suggest that the anion present in solution can influence the inversion rate both through its effect on electrophilicity of the -MgX fragment in solution and through its effect on the carbon-magnesium bond strength.

This same approach may be used to rationalize the dependence of the inversion rate on solvent. Ethers are electron-donor solvents, by virtue of their non-bonding oxygen electrons; as such, they are known to be capable of forming strong dative bonds to positively charged magnesium species. In an ionization-recombination mechanism, solvation of the transition state should be more important than solvation to the ground state, because charge separation in the transition state will be greater. Inversion should therefore proceed more rapidly in a basic ether such as tetrahydrofuran than in a relatively non-basic ether such as diethyl ether, because of the greater capability of the former to solvate the positively charged magnesium fragment in the transition state.

If, on the other hand, the rate of inversion is primarily dependent upon the electrophilicity of the -MgX fragment, inversion should be slowest in the most basic ether: the ability of the basic ether to donate electrons to the magnesium atom should considerably reduce the electrophilicity of this atom.

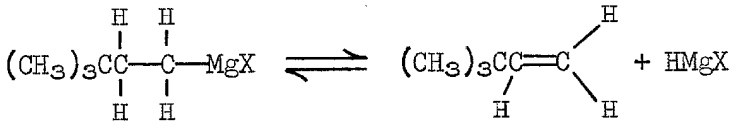
The spectra of Figure 7 indicate the inversion is fast in diethyl ether, slower in tetrahydrofuran, and slowest in diglyme. Consequently, the dependence of inversion rate on solvent character also provides qualitative support for the suggestion that the inversion mechanism is characterized by a molecularity higher than one.

The effect of structure on the rate of inversion has not been investigated carefully. The activation parameters obtained for inversion of 3,3-dimethylbutylmagnesium chloride and 2-phenyl-3-methylbutylmagnesium chloride in ether suggest that inversion is slightly slower in the latter compound. This CH_2-Mg center is probably more hindered than the corresponding center in the 3,3-dimethylbutyl Grignard reagent. Steric interaction between the magnesium atom and β substituents would tend to increase the rate of inversion in a mechanism involving ionization (relief of steric strain in the transition state) but to decrease the rate in the bimolecular mechanism. The direction of this effect is certainly not inconsistent with the bimolecular process, but is not sufficiently well documented to offer it much support. In addition, differences in the rates of inversion in the series 3,3-dimethylbutyl-, 3-methylbutyl-, butyl- appear to be small.

The response of the inversion rate to changes in several variables thus appears to support the suggestion that the mechanism of inversion involves two magnesium atoms in the transition state. However several unknown features of the structure of these Grignard reagents in solution may have combined to make this conclusion spurious. Most important, the effect of any of these variables on the

degree of association of the Grignard reagent in solution is not known.

Two further possibilities for the mechanism of inversion should be mentioned briefly. The first involves a rapid reversible elimination of magnesium hydride from the Grignard reagent, followed by addition of the hydride to the resulting olefin



The second has as its rate determining step a homolytic rather than heterolytic cleavage of the carbon-metal bond

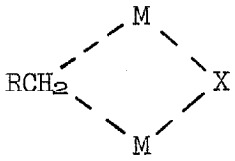
$$RCH_2\text{—}MgX \rightleftharpoons RCH_2\cdot + \cdot MgX$$

Both of these reactions have precedent at high temperatures. Diethylmagnesium, for example, decomposes at temperatures between 175° and 200° yielding magnesium hydride and ethylene; diphenylmagnesium decomposes above 280° with formation of biphenyl (57). Moreover, the isomerization of vinylaluminum compounds has been shown to proceed at a moderate rate at approximately 100° by an elimination-addition mechanism (58).

Magnesium and lithium hydrides are ordinarily not sufficiently electrophilic in ether solutions to add to olefinic bonds. It is however conceivable that the HMgX produced by elimination from a Grignard reagent would have a much higher electrophilicity than it would fully solvated in solution.

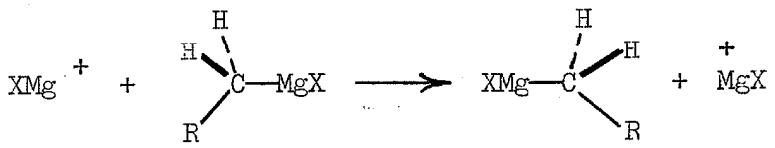
If the mechanism of the inversion reaction bears any resemblance to the electrophilic substitution reactions of organomercury

compounds, it is interesting to speculate on the possible rate of alkyl group migration with retention of configuration. The organomercury compounds commonly exchange through a four-centered transition state



and their rate of exchange with retention of configuration is much greater than that with inversion. It seems possible that this type of transition state might lead to an inversion, if the C-M bonds were highly polarized in the transition state. If the inversion of the organomagnesium compounds proceeds through an intermediate or transition state of this geometry, the rate of metal-metal exchange with retention of configuration would be expected to be much faster than the corresponding rate with inversion.

If inversion depends primarily on the electrophilicity of the magnesium compounds in solution, the relatively small difference in the inversion rates of 3,3-dimethylbutylmagnesium chloride and bis-(3,3-dimethylbutyl)-magnesium is surprising. The major differences in the chemistry of Grignard reagents and dialkylmagnesium compounds suggest that the two have large differences in structure. The simplest way of writing a bimolecular inversion involves participation of magnesium halide in a transition state



geometrically similar to that of an S_N2 reaction. A mechanism of this type would be difficult to write for a dialkylmagnesium compound. (Note however, that the results reported in this thesis do not exclude the possibility that all the inversion observed in the dialkylmagnesium compounds takes place <u>via</u> the catalytic action of small quantities of magnesium halide left unprecipitated by dioxane. Spectral examination of dialkylmagnesium compounds prepared by magnesium-mercury exchange from the corresponding dialkylmercury compounds would be pertinent to this question.)

The transition state drawn above for the inversion is obviously incompatible with Dessy's conclusion that exchange does not occur between the magnesium atom of a dialkylmagnesium compound and the magnesium atom of magnesium halide in the same solution. It is, however, difficult to conceive of a reasonable mechanism for the inversion that rigorously restricts the origin of the magnesium atom bound to carbon <u>after</u> the inversion, to the degree implied by Dessy's experiment.

PART II

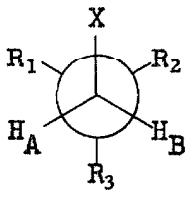
APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY TO THE STUDY OF MOLECULAR ASYMMETRY

INTRODUCTION

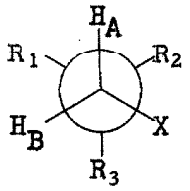
The protons of a methylene or isopropyl group removed by one or more bonds from a center of molecular asymmetry may be magnetically non-equivalent and display AB-type nuclear magnetic resonance spectra (37). The complexity of the spectrum of a compound containing one or more centers of asymmetry is frequently such that it may be very difficult to interpret the spin-spin coupling patterns of groups in close proximity to the asymmetric center in terms of structural features of the molecule. A familiarity with the types of structural groupings which are capable of producing magnetic non-equivalence in adjacent groups is consequently of considerable practical value to anyone using n.m.r. spectroscopy as a structure-determining tool. Interest in the effect of molecular asymmetry on n.m.r. spectra is not however restricted to primarily analytical concerns. The magnetic non-equivalence of a methylene group close to an asymmetric center is capable of providing a sensitive and convenient probe with which to investigate the conformations of the molecule in the region of the asymmetric center; examination of the temperature dependence of this non-equivalence can provide information concerning fast reactions occurring close to the asymmetric center. Moreover, since the effect under consideration is independent of the optical activity of the sample, n.m.r. spectroscopy can be used in suitable compounds to provide the same type of information that optical rotation measurements would provide, without the necessity of resolving the sample.

Two explanations have been advanced to account for the difference in chemical shift of methylene protons in close proximity to a center

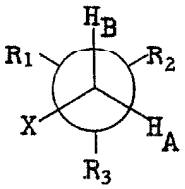
of molecular asymmetry. The first is based on unequal population of the rotational conformations open to the molecule (37). For the three principal conformations of a substituted ethane I, II, III, assuming that interconversion between the three is rapid



I



II



III

$$\langle \nu_A \rangle = \chi_I(\nu_A)_I + \chi_{II}(\nu_A)_{II} + \chi_{III}(\nu_A)_{III} \qquad (1)$$

where χ_n is the mole fraction of rotamer n in solution and $(\nu_A)_n$ is the chemical shift of proton A in rotamer n. Extending equation (1) to include all possible rotamers, and subtracting the analogous expression for $\langle \nu_B \rangle$

$$\langle \nu_A - \nu_B \rangle = \sum_n \chi_n (\nu_A)_n - \sum_n \chi_n (\nu_B)_n$$

$$= \sum_n \chi_n (\nu_A - \nu_B) \qquad (2)$$

If for some preferred conformation M, $(\nu_A - \nu_B)_M \neq 0$, then $\langle \nu_A - \nu_B \rangle$ will be zero only by coincidence. On the other hand, if all conformations are equally populated, i.e. $\chi_N = \chi_M = C$ it is possible to write equation (2) in the form

$$\langle \nu_A - \nu_B \rangle = C \sum_{N,M} \left((\nu_A)_N - (\nu_B)_M \right) \qquad (3)$$

If we then choose the index M such that H_B occupies exactly the same position in rotamer M, relative to R_1, R_2 and R_3 as H_A does in rotamer N, we can say that

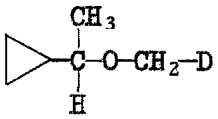
$$(\nu_A)_N - (\nu_B)_N = 0 \qquad (4)$$

to a first approximation. This equation implies that $\langle \nu_A - \nu_B \rangle = 0$. Equation (4) is of central importance in understanding the conformational preference argument. Reduced to its simplest terms it says that the chemical shift of H_A in rotamer I is identical with that of H_B in rotamer II, with the restriction that all the bond angles and bond lengths are the same in the two conformers and that H_A in I and H_B in II occupy the same position relative to R_1, R_2 and R_3. Alternately, (4) may be expressed by saying that the magnetic field experienced by H_A is independent of the magnetic and electric fields at H_B and X.

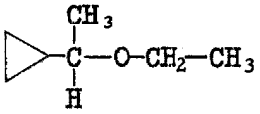
A second explanation may be proposed for the magnetic non-equivalence of methylene protons in close proximity to a center of molecular

asymmetry. Pople (70) and Waugh and Cotton (71) have pointed out that even assuming equal populations and rapid interconversion of the possible conformers of the molecule, the two protons H_A and H_B are always distinct and identifiable, since no two conformers are identical except for interchange of H_A and H_B. Physically, this proposal would take the form of an assertion that equation (4) is not valid: that is, that the chemical shift of H_A in conformer I is not the same as that of H_B in conformer II even if the geometry of the two conformers is restricted as outlined above.

Roberts and co-workers (37d) have attempted to distinguish between the "conformational preference" and "intrinsic asymmetry" arguments by comparing the spectrum of cyclopropylmethylcarbinyl methyl-d_1 ether (IV) with that of cyclopropylcarbinyl ethyl ether (V).



IV



V

They found that the spectrum of the methylene protons of V was an AB-type spectrum, while that of the methylene protons of IV was A_2 (after taking into account spin-coupling of the hydrogens with the deuterium atom). Reasoning that the substitution of a deuterium for the methyl of V should remove all conformational preference of the methylene protons with respect to the asymmetric center, they concluded that the chemical shift between the methylene protons of V was not due to an intrinsic asymmetry of the molecule depending only on its symmetry characteristics,

and suggested that conformational preference is the factor responsible for the magnetic non-equivalence of the methylene protons of IV.

Gutowsky (36) has vigorously attacked this interpretation on the grounds that the characteristics of a C–D bond are so similar to those of a C–H bond that the $-CH_2D$ group of IV would be expected to resemble a $-CH_3$ group in its response to the asymmetric center rather than a $-CH_2CH_3$ group. Consequently, he felt that no conclusions concerning the origin of the asymmetry in V could be drawn from the spectrum of IV.

Gutowsky has suggested that a better approach to the problem of distinguishing between the "intrinsic asymmetry" of a molecule and asymmetry due to conformational factors lies in study of the variation of $\langle \nu_A - \nu_B \rangle$ with temperature. If there were a contribution to $\langle \nu_A - \nu_B \rangle$ which is independent of conformational preference, this contribution should persist at temperatures high enough to populate all of the rotational conformations equally. If, on the other hand, there is no significant contribution to the magnetic non-equivalence of a methylene group from molecular "intrinsic asymmetry," the non-equivalence should go to zero at high temperatures.

Although this proposed experimental separation of intrinsic asymmetry and conformational preference has considerable virtue from a theoretical point of view, it suffers from the practical disadvantage that temperatures sufficiently high to remove all conformational preference of the methylene group with respect to the asymmetric center (i.e., the highest energy eclipsed conformation and the lowest energy staggered conformation must be equally populated to within the limit of experimental

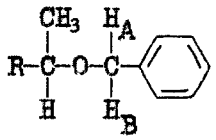
detection) would also be sufficiently high to decompose most organic molecules. Consequently, Gutowsky's one experimental test of this proposal, involving an examination of the chemical shifts and coupling constants of $CF_aF_bBrCFBrCl$ over the temperature range 225° to 465°K, cannot be regarded as meaningful.

The relative importance of conformational preference and intrinsic asymmetry in determining the magnitude of the magnetic non-equivalence of methylene protons close to a center of molecular asymmetry remains uncertain, despite the experiments described above. It should however be emphasized that the question is not whether intrinsic asymmetry or conformation preference should be considered responsible for the magnetic non-equivalence, but rather how much, if any of the observed chemical shift difference should be ascribed to intrinsic asymmetry. There seems little doubt that conformational preference must be the major contributor to the asymmetry in most cases.

This part of this thesis is concerned with an empirical study of the effect of structure and solvent on the magnitude of the magnetic non-equivalence of methylene or isopropyl groups close to a center of molecular asymmetry. As such, its immediate purpose was to provide a guide for the synthesis of compounds to be used in rate studies depending upon the temperature dependence of an AB-type spectrum. However, attempts to reconcile the results obtained with an explanation of the manner in which the asymmetric center exerts its influence on surrounding nuclei suggest that the study of AB methylene groups may provide a sensitive way of examining problems of conformation and solvation in solution.

RESULTS AND DISCUSSION

The Effect of the Structure of the Asymmetric Center on the Magnetic Non-equivalence of an Adjacent Methylene Group. - The experimental approach to this problem was chosen for its simplicity: one structural feature of the asymmetric center was varied, and the response of the chemical-shift difference between the protons of an adjacent methylene group to the changes in this feature determined by analysis of the n.m.r. spectrum of the compound. The compounds chosen for study were formally benzyl ethers of secondary alcohols; their structure is represented schematically by VI:



VI

This general structure was chosen for investigation primarily for its availability from any of several convenient ether syntheses. Compounds of this structure share the advantage that analysis of the AB-type methylene proton spectra to obtain the desired spectral parameters is extremely simple. They suffer from three disadvantages: first, unresolved coupling between the benzyl methylene protons and the adjacent ring protons results in a linewidth of approximately 0.5 cps. for the components of the AB spectrum. Consequently, line positions of the two central components becomes uncertain for values of $\nu_A - \nu_B$ less than approximately 3 cps., due to overlap. Second, introduction of an

ether oxygen atom between the asymmetric center and the methylene group results in a considerable increase in the number of possible conformations of these two centers relative to one another, and considerably complicates attempts to discuss details of their interaction. Third, the presence of a phenyl group in the structure carries with it definite complications stemming from the high magnetic anisotropy of this group. This last feature in particular will be the subject of discussion later in this section.

The groups selected to complete the asymmetric center of VI, i.e. the groups in the position designated by R, were four alkyl groups of varying size (ethyl, isopropyl, cyclohexyl and t-butyl) and two unsaturated groups (phenyl and carboethoxyl). The results of analysis of the methylene proton spectra of these six compounds in solution in carbon tetrachloride, benzene and acetone are summarized in Table I. The chemical shift differences were obtained from solutions approximately 10% in ether; tetramethylsilane was used as internal standard. The chemical shift difference between the methylene protons depends to a small extent on the concentration of ether and on the concentration of tetramethylsilane. The errors introduced by not extrapolating the chemical-shift differences to infinite dilution of both solute and tetramethylsilane are not large enough to influence the relative values reported in Table I, to a significant degree.

The most important feature of these numbers is their suggestion of a correlation between the magnetic non-equivalence of the methylene protons and the size of R, when R is an alkyl group. A crude measure of the size of the R group can be obtained from the A value of the group

Table I

Magnetic Non-equivalence of the Benzylic Protons of Benzyl Methylalkylcarbinyl Ethers of Structure VI

R	$\nu_A - \nu_B$ (cps.) and solvent[a]				A
	carbon tetrachloride	benzene	acetone	pyridine	
Ethyl	5.8	6.6	5.8		1.86[b]
Isopropyl	8.8	9.3	8.6		2.1 [c]
Cyclohexyl	9.7	10.2	9.6		-
t-Butyl	14.8	15.7	14.7		>5.4 [e]
Phenyl	10.2	10.9	2.5	6.0	2.0 [d]
Carboethoxyl	16.5	20.7	11.8	15.2	1.1 [f]

(a) Solutions were 10 ± 2% by volume in solute; the experimental error in the chemical shift values is ±0.5 cps.

(b) N. L. Allinger and S. Hu, J. Am. Chem. Soc., 84, 370-372 (1962).

(c) N. Allinger and S. Hu, J. Org. Chem., 27, 3417-3420 (1926).

(d) N. Allinger, ibid., 27, 4603-4606 (1962).

(e) S. Winstein and N. J. Holness, J. Am. Chem. Soc., 77, 5562-5578 (1955).

(f) E. L. Eliel and M. Granni, Tet. Letters, 97-101 (1962).

(the A value of a group is defined as the difference in free energy in kcal./mole between a cyclohexane ring bearing the group in an axial conformation, and one in which the group occupies an equatorial position) (72). These A values cannot be considered to describe the size of each group in more than a qualitative manner, because of the major differences between the structure of VI and a cyclohexane ring. They do however lend support to the intuitive feeling that the order in size of the alkyl groups of Table I should be t-butyl $\gg$ cyclohexyl > isopropyl > ethyl. The magnitude of the magnetic non-equivalence follows the same order.

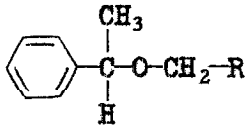
The two unsaturated groups in Table I, phenyl and carboethoxyl, clearly do not follow the same pattern as do the alkyl substituents. The A value of a phenyl group suggests that it is slightly smaller than an isopropyl group; however the magnitude of the magnetic non-equivalence for 1-phenylethyl benzyl ether in carbon tetrachloride and benzene solutions (10.2 and 10.9 cps. respectively) is significantly larger than the corresponding values for isopropylmethylcarbinyl benzyl ether in these solvents (8.8 and 9.3 cps.). In contrast, the value of the magnetic non-equivalence for the phenyl substituted compound is much smaller (2.5 cps.) in acetone solution than that of its alkyl substituted counterpart (8.4 cps.).

The values of the magnetic non-equivalence for carboethoxymethylcarbinyl benzyl ether are even less what would be expected, if the bulk of the substituent R were the only important factor in determining the relative magnitudes of the chemical-shift differences reported in Table I. Carboethoxy has an A value of approximately 1.1, appreciably smaller even than methyl; yet the values of the magnetic non-equivalence in benzene

and carbon tetrachloride solutions are larger for this compound than for t-butylmethylcarbinyl benzyl ether in the same solvents.

These data suggest that an asymmetric center containing an unsaturated group will be expected to behave differently than one containing only saturated groups. We shall see later that this difference in behavior originates in the high sensitivity of the compounds containing an aryl group in the asymmetric center to the dielectric constant of the solvent; the reason for this sensitivity will be discussed in terms of a detailed picture of the conformational populations of the molecules, after the effect of solvent on the magnetic non-equivalence of the protons has been presented in detail.

The dependence of the magnetic non-equivalence on structural variation involving the substituent directly bonded to the methylene group does not seem to follow the pattern suggested by Table I, although fewer compounds have been examined. The chemical shifts between the methylene protons of four ethers of structure VII are summarized in



VII

Table II. In benzene solution, when R is an alkyl group, the magnetic non-equivalence of the methylene protons again increases as the size of R increases. When R is phenyl, however, the non-equivalence is larger than when R is t-butyl.

Table II

Magnetic Non-equivalence of the

Methylene Protons of Ethers of Structure VII

R	$\nu_A - \nu_B$ and Solvent[a]		
	carbon tetrachloride	benzene	acetone
Methyl	- [b]	~3.1	- [b]
Isopropyl	<0.2	4.1	1.4
t-Butyl	<0.2	6.9	<0.2
Phenyl	10.2	10.9	2.5

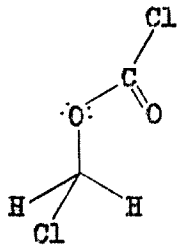
(a) Solutions were 10 ± 2% by volume in solute.

(b) These spectra were not explicitly analyzed; however, an upper limit of approximately 2 cps. can be placed on $\nu_A - \nu_B$ by inspection.

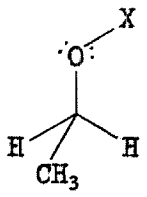
In order to discuss the data of Tables I and II, in terms of the conformation of the methylene groups with respect to the asymmetric center, it would be helpful to know the details of the stereochemistry about an ether oxygen atom. In particular, an estimate of the "size" of the non-bonding electrons on the oxygen atom would be useful. The C-O-C bond angle has been determined for diethyl ether from electron diffraction data, and found to be 108 ± 3° (73); this angle suggests that the hybridization at the ether oxygen atom is close to tetrahedral. X-ray crystallographic or electron diffraction data pertaining to the configuration around an ether oxygen atom are unfortunately not available.

However, some structure work has dealt with the related problem of configuration around the ether oxygen atom of esters.

Kashima has carried out an electron diffraction study of chloromethyl chloroformate and has found that the chlorine atom of the chloromethyl group is <u>trans</u> to the carbonyl carbon atom across the oxygen-carbon single bond (IX) (74). The same stereochemical result has been reported



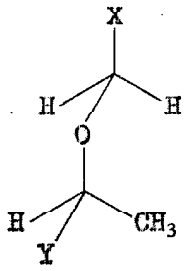
IX



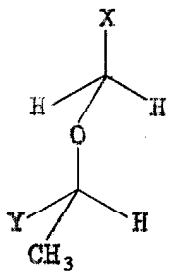
X

for the configuration about the ether oxygen atom in diethyl terephthalate (75) and in potassium ethyl sulfate (76) (X). To the extent that the stereochemistry about the ether oxygen atom of these compounds can be considered a model for the stereochemistry about the ether oxygen atom of a benzyl ether in solution, these structure determinations suggest that a lone pair of electrons on oxygen is smaller than an alkyl substituent attached to oxygen.

An ether of the type examined in this work can theoretically exist in nine possible conformations (there are two C-O bonds, and three possible rotational conformers around each). If the ether contains a center of molecular asymmetry, all of these conformations will be distinct. These nine conformations are represented schematically in Fig. 1.



1



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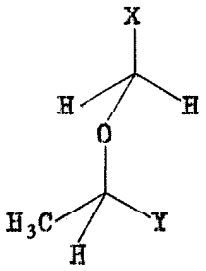

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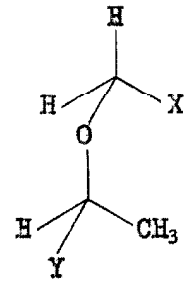

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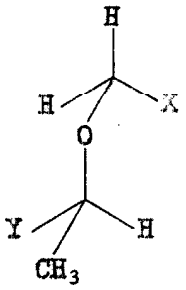

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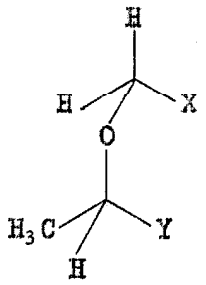

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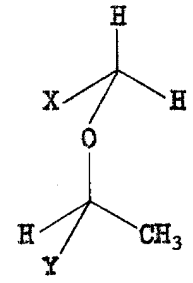

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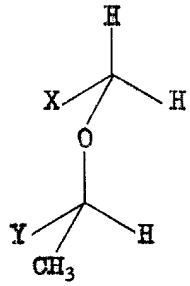

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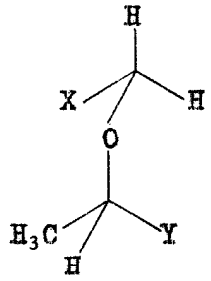

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Fig. 1. Possible rotational conformations of an ether containing one center of asymmetry.

The structure determinations mentioned above suggest that conformation 1 should be of lowest energy, provided that the Y group is larger than the methyl group, and provided that steric interactions completely determine the relative energies of the conformations. We will suggest later that other interactions, particularly those depending on dispersion and induction forces, may be important when the groups X and Y are polarizable. For certain of the molecules examined, however, steric interactions do appear to dominate.

Conformation 1 places the large X and Y groups gauche to the non-bonding electron pairs on the oxygen atom and trans to the larger alkyl group, and should consequently be sterically most favored. If the size of the Y group is close to that of a methyl group, conformation 2 should be significantly populated. Conformations 5 and 7 and possibly 4 and 8 may be populated to a small extent for small X and Y groups; the populations of conformations 6 and 9 will probably be very small, if only steric factors are important.

It is difficult at this point to make more quantitative estimates of the relative energies of conformers 1-9, because good model systems have not been investigated. For X and Y groups of moderate size, as phenyl or methyl, one can estimate from the available data on substituted butanes and pentanes that the change in energy on going from conformation 1 to conformation 2 will be no more than one or two kcal./mole (77).

We have assumed in this discussion that steric interactions between the two groups attached to oxygen determine the relative energy of the possible conformations. On this assumption, conformation 1 is of lowest energy when X and Y are larger than $-CH_3$; moreover, increasing the size

of X and Y should increase the extent to which conformer 1 is favored over the other possible conformers.

Examining Tables I and II, and restricting attention for the moment to those compounds in which the group R being varied is an alkyl group, it appears that the larger the group R, the larger the magnetic non-equivalence of the methylene protons. This observation, when taken in conjunction with the foregoing discussion of the possible conformations for these ethers, suggests that the observed chemical shift between the methylene protons can be associated with a conformation of type 1, 4 or 7. The larger the group Y or X, the more highly these conformations are populated with respect to the other conformations, and the larger is the associated chemical shift between the methylene protons.

The two compounds in Table I having R as an unsaturated group clearly do not fall into this simple classification. When R is phenyl, the magnetic non-equivalence of the methylene protons is slightly larger than when R is isopropyl, although a phenyl group is probably slightly smaller than an isopropyl group. When R is carboethoxy, the non-equivalence is larger than when R is t-butyl, although the carboethoxy group is much the smaller of the two.

The exceptional behavior of the carboethoxy group can be rationalized relatively simply. A comparison of the A values given in Table I indicates that carboethoxy is a significantly smaller group than methyl. Hence, on steric grounds, a conformation of type 2 would be of lower energy for this group than a conformation of type 1. Moreover, conformation 1 places the carboethoxy group gauche to both of the electron pairs on oxygen; conformation 2 places it gauche to one and trans to the other.

Consideration of the electrostatic interaction between the oxygen atoms in these configurations suggests that the latter would be of lower energy (77). Configuration 2 places the carbonyl group closer to one of the methylene protons than the other, and the well-known anisotropy of this group would be expected to produce a large chemical shift between the two.

The difference in the methylene proton chemical-shift difference for R = phenyl and R = isopropyl is less simply explained, and the greater part of the remainder of this discussion will be spent in attempting to construct a convincing explanation for these values. By way of background, it will first be useful to describe the solvent dependence of the spectra of these and other compounds.

The Effect of Solvent on the Non-equivalence of the Methylene Protons (78). - The chemical shifts between the methylene protons of three alkyl substituted ethers of structure VI are given in Table III, for seven solvents of varying dielectric constant, acid strength, and base strength. The most remarkable feature of these data is the insensitivity of the methylene chemical-shift difference to the nature of the solvent. Neither change in dielectric constant (from 45 for dimethylsulfoxide to 2.05 for cyclohexane), in acid or base strength or in size has an appreciable effect on the magnitude of the chemical-shift difference. This insensitivity to solvent is particularly striking when contrasted with the high sensitivity to solvent exhibited by 1-phenylethyl benzyl ether (Table IV), and by 1-phenylethyl neopentyl ether (Table V).

Discussion of the effect of solvent on the chemical shift of the adjacent protons is a very complicated matter. In order to simplify

Table III

Solvent Dependence of the Magnetic Non-equivalence of the Methylene Protons for Alkylmethylcarbinyl Benzyl Ethers of Structure VI

R	Ethyl	Isopropyl	t-Butyl
Solvent			
Carbon tetrachloride	5.8	8.8	14.8
Benzene	6.6	9.3	15.7
Cyclohexane	5.7	8.6	
Acetone	5.7	8.6	14.7
Dimethyl sulfoxide	4.9	8.2	15.1
Acetic acid	5.4	8.0	
t-Butyl alcohol			14.9

an understanding of this discussion, we will first state briefly the major points which will be covered and conclusions which will be reached.

The chemical shift between the methylene protons in close proximity to the center of asymmetry in these ethers will be discussed in terms of possible contributions from the magnetic anisotropy associated with the carbon-carbon single bonds in the asymmetric center, and with the anisotropy of the phenyl rings arising from the phenyl ring-current. The ring-current effect of the phenyl ring bonded to the methylene group will be suggested to be larger than the other effects, and the striking solvent effects observed for the ethers containing unsaturated groups both in the asymmetric center and bonded to the methylene group will be

Table IV

Chemical Shift between the Methylene Protons of 1-Phenylethyl Benzyl Ether as a Function of Solvent

Solvent	$\nu_A - \nu_B$ [a]	Dielectric Constant [b]
n-Pentane	10.1 cps.	1.84
Cyclohexane	10.1	2.05
Benzene	10.9	2.28
Carbon tetrachloride	10.2	2.24
Dioxane	6.9	2.21
Diethyl ether	9.0	4.33
Chloroform	8.6	5.05
Chlorobenzene	8.2	5.94
Methyl iodide	6.0	7.0
Aniline	7.8	7.25
o-Dichlorobenzene	7.2	7.47
t-Butyl alcohol	5.7	10.9
Pyridine	6.1	12.5
Acetic anhydride	4.6	20.5
Acetone	2.5	21.4
Cyanobenzene	3.8	25.2
Nitrobenzene	3.8	36.1
N,N-Dimethylformamide	2.5	36.7
Nitromethane	3.1	37.5 [d]
Dimethyl sulfoxide	2.0	45 [c]

Table IV (Contd)

Solvent	$\nu_A - \nu_B$ (a)	Dielectric Constant (b)
Formic acid	9.9	58.5
Acetic acid	10.3	6.29
Ethanol	7.4	24.3

(a) Tables of chemical shifts relative to tetramethylsilane, and coupling constants for the aliphatic parts of this molecule will be found in the experimental section.

(b) Handbook of Chemistry and Physics, 44th Edition.

(c) Merck Index, 17th Edition.

(d) J. Hine, "Physical Organic Chemistry," 2nd Edition, McGraw-Hill Book Co., Inc., 1962, p. 39.

Table V

Chemical Shift between the Methylene Protons of 1-Phenylethyl Neopentyl Ether as a Function of Solvent

Solvent	$\nu_A - \nu_B$
Benzene	6.6 cps.
Toluene	5.9
Cyclohexane	4.6
n-Pentane	4.5
Bromobenzene	3.0
Carbon disulfide	<1
Chloroform	<1
Carbon tetrachloride	<1
Nitrobenzene	<1
Pyridine	<1
Formic acid	<1
Dimethyl sulfoxide	<1

discussed in terms of the effect of solvent character on the dispersion and induction forces between the unsaturated groups. Evidence for the existence of a preferred conformation of the phenyl group bonded to the methylene group with respect to this methylene group will be discussed in the specific case of 1-phenylethyl benzyl ether.

Before discussing details of the factors responsible for the difference in the magnetic shielding at the two methylene protons, we should first establish the broad features of the system in which we are interested. The observed chemical shielding σ of each methylene proton can conveniently be divided into two parts

$$\sigma = \sigma_e + \sigma_d$$

where σ_e is the shielding due to the electrons in the carbon-hydrogen bond and σ_d is the shielding due to parts of the molecule distant from the methylene carbon-hydrogen bonds (79). The apparent electronegativity of the carbon to which the hydrogen is bonded is the most important contributor to σ_e; factors determining σ_d include bond anisotropies of bonds in the vicinity of the hydrogen being observed, ring-current effects and shieldings due to solvent molecules.

It would seem very unlikely that the local chemical shielding term σ_e contributes in an important way to the chemical shift between the methylene protons of the ethers being examined, because the two carbon-hydrogen bonds would be expected to have a very similar character in these compounds. We have not examined specifically the bonding in these ethers; however, in four similar compounds there is evidence that the carbon-hydrogen bonds to the magnetically non-equivalent groups are very

similar. Diethyl sulfoxide, diethyl sulfite, isopropyl methyl sulfoxide and isopropyl methyl carbinol are observed to have equal ^{13}C-H coupling constants between the methylene carbon atom and the two methylene protons (in the first two compounds) and between the methyl carbon atoms and the methyl protons in the last two. If the differences in the shielding at the non-equivalent protons of these compounds were due to a difference in the orbital electronegativity of the carbon bonding orbitals directed toward them (in other words, to a difference in the s character of these orbitals) one would expect this difference to be reflected in the ^{13}C-H coupling constants between these protons and their directly-bonded carbon atoms (80). The observation of identical ^{13}C-H coupling constants between corresponding non-equivalent protons thus suggests that σ_e is not a major contributor to the difference in chemical shift between the methylene hydrogens. The difference in shielding at the magnetically non-equivalent protons is therefore due primarily to the circulation of electrons in parts of the molecule well removed from the methylene groups.

Proceeding now to a discussion of the factors which contribute to σ_d, we consider first the ethers which have only alkyl groups in the asymmetric center.

Several observations suggest immediately that solvent effects are not responsible for the major part of the magnetic non-equivalence of the methylene protons in these ethers. Table III is most important in indicating that the solvent does not play the dominant role in determining the magnitude of the magnetic non-equivalence. The variation in the chemical shift values for each compound reported in this table is less than 1.5 cps., for a variety of solvents. Particularly noteworthy in

the solvents given in Table III are acetic acid, benzene, and dimethyl sulfoxide. The observation that chemical shifts in acetic acid are no larger than those in carbon tetrachloride or cyclohexane suggests strongly that specific solvent interaction involving the ether oxygen atom is of minor importance. The unexceptional value of the non-equivalence in benzene solutions indicates that magnetic anisotropy originating in the solvent molecule is not a major contributor to the magnetic non-equivalence. (It should be pointed out here that the value of the non-equivalence for a benzene solution of the compounds in Table III and all other compounds examined is always 0.5-5 cps. larger than for solutions in other solvents. In the present discussion, this effect is clearly minor; it does suggest that the magnetic anisotropy of the solvent can be a significant contributor to the methylene non-equivalence.) The value of the non-equivalence in dimethyl sulfoxide and in cyclohexane solutions indicates that this chemical shift is insensitive to the dielectric constant of the solvent. Thus, at the simplest level of discussion, it seems justified to neglect the effect of solvent on the degree of non-equivalence of the methylene protons.

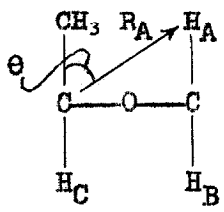
If the solvent molecules are unimportant in determining the chemical shift between the methylene protons, the origin of the asymmetry effect must be intramolecular. The two most reasonable sources of the difference in shielding at the methylene protons are electrons circulating in the sigma bonds of the molecule, and electronic circulations associated with the unsaturated centers [i.e., ring-current effects from the phenyl groups (81)].

The importance of the magnetic anisotropy of the carbon-carbon sigma bond has been the subject of extensive (if inconclusive) theoretical (82) and experimental (83) study. The contribution σ_a to σ_d resulting from the circulation of electrons induced by the static external magnetic field is usually expressed by the equation (84) for a carbon-carbon sigma bond

$$\sigma^{C-C} = \Delta\chi/3R^3(1 - 3\cos^2\Theta)$$

where $\Delta\chi$ is the difference between the magnetic susceptibility of the bond measured parallel and perpendicular to its axis, R is the distance between the center of the bond and the proton under consideration, and Θ is the acute angle between the axis of the bond and the radius vector of R. Experimental determinations of $\Delta\chi$ have ranged from 2×10^{-30} cm.^{3} molecule^{-1} (85) to more recent values of approximately 7×10^{-30} cm.^{3} molecule^{-1} (83); theoretical values are smaller.

Using 7×10^{-30} cm.^{3} molecule^{-1} as the value of $\Delta\chi$, we can calculate the magnitude and direction of the chemical shift expected in any conformation of the ether. We examine here the magnetic non-equivalence of the methylene protons in conformation 1 of Fig. 1, due to the anisotropy of the CH_3–C bond [for simplicity we adopt the common assumption (83,85) that a carbon-hydrogen bond is isotropic]. Considering only the fragment



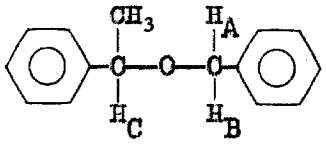
R_A = 2.2 Å
Θ_A = 85
R_B = 2.9 Å
Θ_B = 50

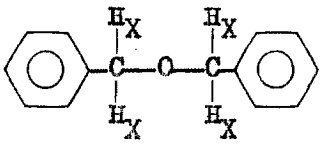
and using the parameters indicated (obtained from Dreiding models) in the equation for σ^{C-C}, we obtain for example

$$\sigma_A^{C-C} = \frac{7 \times 10^{-30}}{3(2.2\times10^{-8})^3}(1 - 3\cos^2 85^\circ)$$

Using this model, σ_A = 0.21 ppm. and σ_B = -0.01 ppm. In other words, the anisotropy of the C–CH_3 bond should shift H_A approximately 12 cps. to higher field, and H_B approximately 1 cps. to lower field.

The choice of an appropriate model compound with which to judge the reasonableness of these calculated values is a difficult one. Here we have compared the chemical shifts of the methylene and methinyl protons of 1-phenylethyl benzyl ether with the methylene protons of dibenzyl ether.





These relative chemical shifts were obtained by analysis of a mixture of the two ethers in the indicated solvent, in order to obtain accurate relative chemical shifts. The zero of frequency is arbitrarily chosen as $(\nu_A - \nu_B)/2$. (No stereochemistry is to be implied from the labeling of H_A and H_B.)

These values indicate that the methylene protons of 1-phenylethyl benzyl ether occur at higher field than those of dibenzyl ether, in

qualitative agreement with the calculation made on the basis of carbon-carbon bond anisotropy, assuming that conformation 1 is most highly populated. Quantitatively, the shifts predicted are significantly smaller than those observed. Table VI indicates that the mean chemical shift of H_A and H_B (neglecting the values in benzene) is approximately 9 cps. upfield from H_X; the calculated values suggest that approximately 6 cps. would be expected.

Table VI

Chemical Shifts[(a)] of Selected Protons of 1-Phenylethyl Benzyl Ether and of Dibenzyl Ether

Solvent	ν_A	ν_B	ν_C	ν_X
Benzene	-5.7	5.7	2.9	5.0
Carbon tetrachloride	-5.6	5.6	5.0	9.5
Pyridine	-3.6	3.6	6.5	8.1
Diethyl ether	-4.4	4.4	6.4	9.5
Acetone	0.0	0.0	9.8	10.9

(a) A positive chemical shift indicates a shift to lower field than the frequency zero. Chemical shifts are in cps.

Despite this quantitative disagreement between calculated and observed values for the non-equivalence, an explanation of magnetic non-equivalence based on the magnetic anisotropy of the carbon sigma bonds of the asymmetric center might seem an attractive basis for discussing

the data in Table III. On the basis of such an explanation, large values for the non-equivalence would be associated with a high population of conformation 1. Significant population of the other conformations, and in particular conformation 2, would be expected to reduce the non-equivalence, because these conformations reverse the relative positions of the methylene protons with respect to the sigma bonds in the asymmetric center. Hence, R = t-butyl would have a large value for the non-equivalence because its conformational preference for conformation 1 would be large. By the same token, R = ethyl would be relatively small, because both conformations 1 and 2 would both be significantly populated.

Unfortunately, there is evidence that this explanation is probably not the most important one. The most important factor in determining the magnitude of the methylene proton non-equivalence on this basis should be the relative size of the groups attached to the asymmetric center and the methylene group. If this hypothesis were correct, one would predict that replacing either of the phenyl groups of 1-phenylethyl benzyl ether with an isopropyl group should have little effect on the magnitude of the non-equivalence, because a phenyl group and an isopropyl group have approximately the same size. Table I indicates that interchanging phenyl and isopropyl has little effect on the methylene proton non-equivalence, when the change occurs in the asymmetric center, in a low dielectric constant solvent. However, when the phenyl group bonded to the methylene group is replaced by an isopropyl group, the magnetic non-equivalence of the methylene protons is reduced drastically (Table II). This observation suggests that much of the non-equivalence of the methylene hydrogens of these ethers should be attributed to the phenyl group

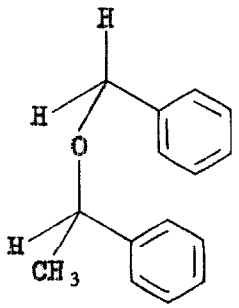
directly bonded to the methylene group.

The phenyl groups in these ethers might exercise their influence in one of two ways: Through specific interaction with solvent (i.e., formation of complexes with definite stereochemistry with the solvent molecules), or through ring-current effects. Although the first explanation has been used with varying degrees of success by other workers to explain the solvent dependence of chemical shift data (86), previously discussed evidence has suggested that specific solvent-solute interactions are not dominant in determining the methylene protons non-equivalence. We will now consider the possible magnitude of phenyl ring-current effects.

Johnson and Bovey (81) have calculated the shielding of a proton in the vicinity of a phenyl ring by considering the precession of the π electrons in two circular regions above and below the plane of the aromatic ring, under the influence of the component of the static magnetic field perpendicular to the ring.

Measurements of Dreiding models indicate that the average distance of the methylene protons of 1-phenylethyl benzyl ether from the center of the closer phenyl ring is approximately 3.5 Å; when one methylene proton is in the plane of the ring, the second is approximately 0.9 Å above it. With these distances, it is possible to estimate from Fig. 1 of reference (81) that the maximum chemical shift between the two methylene protons due to the ring current of the phenyl group bonded to the methylene group will be approximately 0.15 ppm. (9 cps.), and will occur when one proton is in the plane of the ring. (The radius of the benzene ring was taken equal to 1.4 Å in these calculations.)

The chemical shift due to the ring current of the benzene ring attached to the center of asymmetry will of course depend upon the conformation. In conformation 1, the distance between the methylene protons and the center of the ring is approximately 5.2 Å, and the maximum value for the difference in chemical shift due to this ring will be less than 1 cps. (The maximum difference again occurs when one proton is close to the plane of the ring, and the second is relatively far from this plane.) The effect of ring-current in the phenyl group attached to the asymmetric center on the chemical shift between the methylene protons will thus be small in conformation 1, and by similar reasoning in conformations 4 and 7. In conformations of the type 8 (drawn below)



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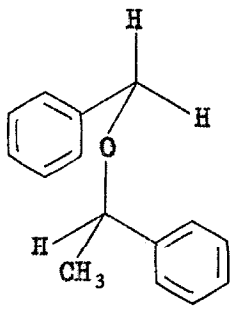

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the difference in chemical shift due to ring B can be estimated to be approximately 3 cps., by the same procedure of measuring the appropriate distances on a Dreiding model and consulting reference (81). In contrast the B ring in conformation 5 will produce a chemical-shift difference between the methylene protons of approximately 30 cps. Physically the difference between 5 and the other less effective conformations is that the B phenyl ring in this conformation lies very close to one of the

methylene protons.

We have observed previously that the data of Table I suggest strongly that the difference in chemical shift between the methylene protons in these ethers is not due primarily to the ring current in the phenyl group attached to the asymmetric center. The principal support for this suggestion was the observation that replacing this phenyl group with an isopropyl group resulted in only a small (approximately 2 cps.) decrease in the magnetic non-equivalence of the methylene protons. From this evidence and from the estimates made above of the magnitudes of the non-equivalence to be expected in the major types of conformations, we conclude that conformations resembling 5 (i.e. those having one methylene hydrogen close to the B phenyl ring) are not highly populated in solution, because these conformations are predicted to have a large value of the non-equivalence, originating in the ring-current of the phenyl group attached to the asymmetric center.

The preceding discussion suggests that the factor responsible for the major part of the methylene proton non-equivalence in the benzyl ethers studied is a preferred conformation of the methylene group with respect to the plane of the nearer phenyl ring, such that one methylene proton lies in the plane of the ring and the second is situated appreciably out of this plane. The ring-current of a phenyl ring located in the asymmetric center contributes little to this chemical shift.

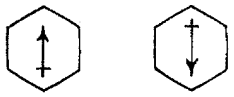
Models of the benzyl ethers suggest that the phenyl group in conformation 1 should be able to rotate freely around the $CH_2-\phi$ bond. The conformations which seem most likely to induce a conformational preference of the phenyl group with respect to the asymmetric center are those in

which the benzylic phenyl ring is close to the asymmetric center: in other words, conformations of the type 5 and 7.

If the populations of these conformations determine the magnitude of the non-equivalence, it should be possible to rationalize the solvent dependence of the ethers on the basis of changes in conformational populations. In attempting this rationalization, we first repeat two important experimental observations. First, the non-equivalence of the methylene protons of those ethers containing only alkyl groups in the asymmetric center is independent of solvent; only ethers having unsaturated groups both on the asymmetric center and on the methylene group display pronounced solvent dependence. Second, the ethers containing unsaturation on both sides of the molecule behave anomalously in solvents of high dielectric constant.

These two observations suggest that in a high dielectric medium there exists an interaction between the two unsaturated centers which is of sufficient energy to have a significant effect on the conformational populations of the molecule. In particular, dispersion and induction (87) interactions between the two phenyl groups would be expected to be more important in high than in low dielectric constant solvents. Dispersion and induction interactions are both electrostatic dipole-dipole interactions. In the molecules of interest, a net attractive force between the phenyl rings might arise from either (87). A dispersion interaction between the two benzene rings would originate in the random "zero point motions" of the electrons in one ring. Although the dipole moment of each ring is small on the average, these electronic motions may result in large randomly oriented instantaneous dipole moments. The

instantaneous electric dipole in one ring is capable of inducing a corresponding dipole in the second ring, either directly [represented schematically by (a)] or <u>via</u> a solvent molecule (b); (here the circle represents the solvent molecule).

(a) 

(b) 

The energy of the interaction represented by (a) can be described by an equation of the form

$$E \simeq -\tfrac{3}{4} I \frac{\alpha^2}{R^6}$$

if we assume that a phenyl ring is spherically symmetrical. In this equation, I is the ionization potential of the phenyl ring, R is the distance between the rings, and α is the polarizability of the ring

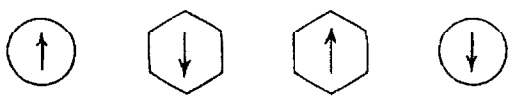
$$\alpha \simeq \frac{2e^2}{3I} \sum_{J} \left| R_{Jo} \right|^2$$

Here e is a unit charge, the R_{jo} are integrals of the form

$$R_{jo} = 3(\phi_j \left| \underset{\sim}{X} \right| \phi_o)$$

ϕ_j and ϕ_o are wave functions of the phenyl ring, and $\underset{\sim}{X}$ is the operator giving the sum of the coordinates of all the electrons in the phenyl group in a given direction (in other words, the displacement of the electrons from their average position in the ground state ϕ_o). The pertinence of these formulas to the present discussion is that they predict that the dispersion energy E will be proportional to 1/I. We can assume that I will be smaller, the higher the dielectric constant of the medium, since I is a measure of the work required to move an electron from the molecule to an infinite distance. Consequently, E should be larger in a medium of high dielectric constant.

Induction interactions between the two phenyl rings would arise in an indirect manner. A dipole moment would be induced in one ring, by the permanent dipole of a solvent molecule. The dipole induced in one ring might then induce an opposed dipole in the second phenyl ring, or it might interact with a dipole in the second ring induced by a second solvent molecule. Either interaction should lead to an attraction between the two rings. High dielectric constant solvents should be



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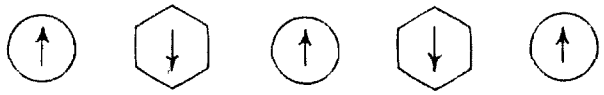
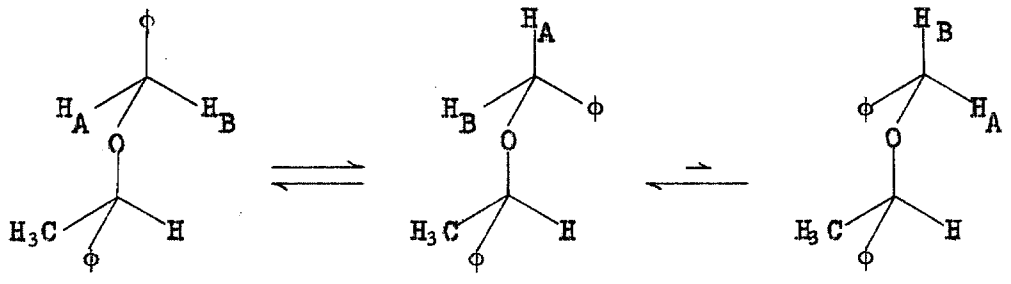


more efficient in inducing these types of interaction than low dielectric solvents.

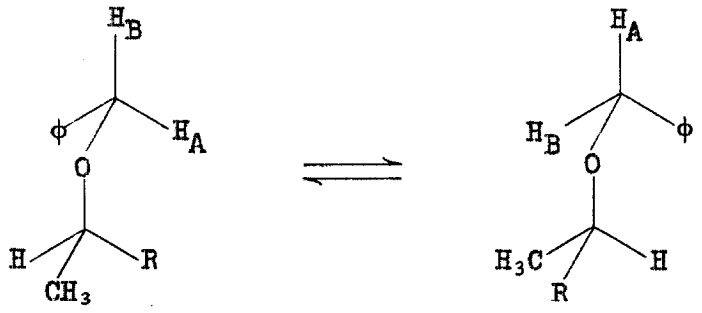
This very qualitative discussion suggests that both dispersion and induction forces between the two phenyl rings in 8 should be larger in high dielectric constant solvents. With this rationale in mind, we now propose a tentative explanation for the solvent dependence of the magnetic non-equivalence of the methylene protons of 1-phenylethyl benzyl ether. In solvents of low dielectric constant, the dispersion interaction mentioned above might be unimportant, relative to steric factors, in determining the populations of the conformations of the ether. Because only the conformation of the phenyl group with respect to the methylene hydrogens is important in determining the magnitude of the chemical shift between them, we write



1 4 7

Conformation 1 contributes nothing to the non-equivalence, because the phenyl group near the methylene protons can rotate freely. The magnitude of the non-equivalence will be determined by the extent to which conformation 4 is preferred to 7. If steric factors are dominant, this preference will be determined by the size of the groups on the asymmetric center. If the methyl group is small relative to the phenyl group, the conformation at the asymmetric center will be the one indicated above, because the largest group will be trans to the benzyl group across the C–O bond. Consequently, the relative populations of 4 and 7 will be determined by the magnitude of the interaction of the benzylic phenyl group with the methinyl hydrogen atom and the methyl group.

We have considered only one conformation at the asymmetric center. Other conformations (for example 5) will tend to reduce the magnitude of

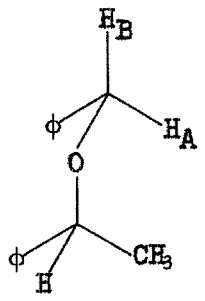


5 7

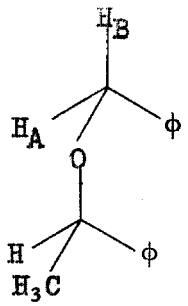
the non-equivalence, because the effect of the phenyl group on the two methylene protons will be opposite in 5 and 7 (to a first approximation). The larger the group R, the more favored will be conformer 7, and correspondingly the greater the value of the non-equivalence. This

rationalization is in accord with the data of Tables I and III, in which the size of the groups on the asymmetric center seem to determine the magnitude of the magnetic non-equivalence.

We suggest that in high dielectric constant solvents, steric interactions in 1-phenylethyl benzyl ether are less important than dispersion and induction interactions between the two phenyl groups; in other words, that conformations 6 and 8 are populated to a greater extent



6



8

than 5 and 7. If 6 and 8 are highly and approximately equally populated, the non-equivalence should be small, because the preference of the methylene protons with respect to the plane of the near phenyl ring will be reversed on interconverting the two conformations.

Conformations 6 and 8 must be approximately equally populated in order for this proposal to explain satisfactorily the small chemical shifts observed in high dielectric constant solvents: interactions involving the methyl group must not confer a large preference on either conformation 6 or 8. Examination of models suggests that this approximation may be valid for the methyl group, but would not be for a larger

group such as an isopropyl group. In accordance with this view, the chemical shift between the methylene protons of phenylisopropylcarbinyl benzyl ether shows the same qualitative dependence on dielectric constant as does that of 1-phenylethyl benzyl ether, but does not go to zero in high dielectric constants solvents (Table VII).

Table VII

Solvent Dependence of the Methylene Proton Chemical Shift Difference of Phenylisopropylcarbinyl Benzyl Ether

Solvent	
Benzene	17.6 cps.
Carbon tetrachloride	16.0
Chloroform	14.5
Diethyl ether	14.4
Pyridine	14.4
Acetone	9.8
Dimethyl sulfoxide	8.7

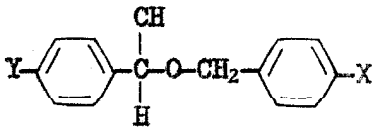
Two interesting observations should be mentioned in connection with this proposed explanation for the solvent dependence of the magnetic non-equivalence of the methylene protons of these compounds. The influence of the solvent on the conformational populations of the ethers has been discussed only in terms of its effect on attractive forces between

the polarizable phenyl groups; the solvent dielectric constant can however also have an effect on the populations of conformations having different dipole moments. Neglect of this factor is probably not serious in any of the ethers discussed so far, because all of the conformations will have approximately the same dipole moment. If, however, a change in conformation were accompanied by a change in dipole moment, the influence of the dielectric constant in determining the relative energies of the different dipole moments should be taken into account.

We have compared the chemical shifts of 1-p-chlorophenylethyl benzyl ether and 1-phenylethyl p-chlorobenzyl ether with 1-phenylethyl benzyl ether in several solvents. The results are tabulated in Table VIII.

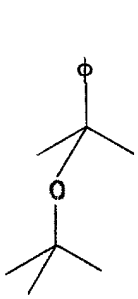
Table VIII

Solvent Dependence of the Difference in Chemical Shift of the Methylene Protons of Ethers

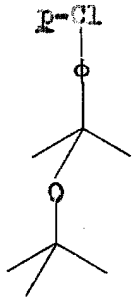


Solvent	X = H; Y = H	X = Cl; Y = H	X = H; Y = Cl
Benzene	10.9 cps.	10.3	10.1
Carbon tetrachloride	10.2	9.1	9.3
Diethyl ether	9.0	7.1	7.5
Pyridine	6.1	4.3	5.2
Dioxane	6.9		6.2
Acetone	2.5	<1	<1
Dimethyl sulfoxide	2.0	<1	

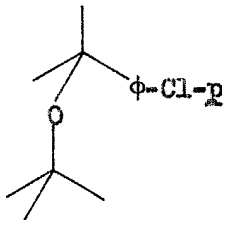
The dipole moments for the different types of conformations for the chlorinated ethers can be calculated crudely by neglecting all bond moments except for those due to the C–O and C–Cl bonds, [taken as 1.2 D and 2.0 D respectively (88)] and measuring bond angles from models. The values obtained for the molecular dipole moments are



$\mu \simeq 1.4D$



$\mu \simeq 3.0D$



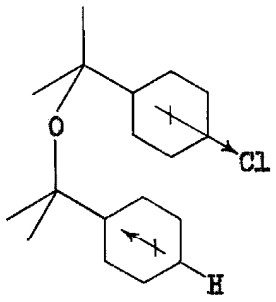
$\mu \simeq 1.8D$

The value for all conformations of the unsubstituted ether (X = Y = H in Table VIII) will be the same, in this approximate treatment.

These dipole moments suggest that the population of conformation 1 should be relatively smaller in low dielectric constant solvents than 5 or 7, because the higher dipole moment conformation should be of relatively higher energy in the low dielectric medium. Consequently the value of the non-equivalence would be expected to be greater for the p-chloro substituted ethers in each solvent; it is actually observed that the chlorine-substituted ethers have slightly smaller values of the non-equivalence.

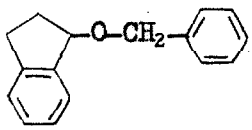
One possible rationalization for this observation can be constructed using the approach outlined above to explain the low value of the magnetic non-equivalence in high dielectric constant solvents.

Substituting the p-hydrogen of either phenyl ring of 1-phenylethyl benzyl ether with a chlorine should not change the steric requirements of the ring; it should however give the ring a large dipole moment. Consequently the ability of the substituted ring to induce an opposing dipole in the unsubstituted ring should be large, even in non-polar solvents. Conformations of the type 6 and 8 might therefore be important



for the chlorine substituted ethers, even in low dielectric constant solvents. For reasons outlined previously, extensive population of these conformations is expected to reduce the magnetic non-equivalence of the methylene hydrogens. Dipole moment studies of these chlorine-substituted ethers could be very pertinent to this question.

A second puzzling observation is less easily rationalized on the basis of the present hypotheses. The benzyl methylene protons of 1-indyl benzyl ether (89) are magnetically equivalent in all solvents. In light of the close structural similarity of this ether to 1-phenylethyl benzyl



ether, this result is difficult to explain. Examination of models of the former compound reveals two possibly pertinent details. First, close approach of the two phenyl groups in this ether is impossible. Second, the methylene group in the 2 position of the indane ring appears to have smaller steric requirements than the methyl group of 1-phenylethyl benzyl ether. The latter fact may be sufficient to explain the small asymmetry in this ether.

Brief mention should be made of the possibility of solvent dependence of the methylene proton non-equivalence originating in the "reaction field" (90) at the methylene group, due to the C-O-C electric dipole. According to Buckingham's theory, the C-O-C dipole would polarize the surrounding medium, thereby inducing a second electric field, the reaction field E, at the solute. This field is related to the dielectric constant of the solvent by an equation of the form (90)

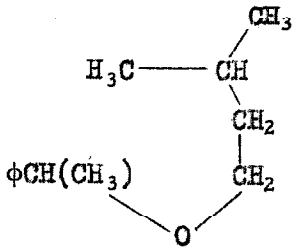
$$E \propto \frac{\epsilon - 1}{\epsilon + \frac{1}{2}n^2}$$

where ϵ is the solvent dielectric constant and n is the index of refraction of the solute as a liquid. If the two methylene protons are not symmetrically placed with respect to the molecular dipole moment, the component of the reaction field along each C-H bond axis will be

different in magnitude. Since this component of the field can influence the chemical shift of the protons by shifting the electron density along the O-H bond axis, the relative chemical shift of the two protons would be expected to depend on the solvent dielectric constant.

The observation that the magnetic non-equivalence of the methylene protons of the ethers containing only alkyl groups at the asymmetric center varies very little with solvent dielectric constant suggests that the reaction field effect is probably not of major importance in these ethers, and by analogy, in 1-phenylethyl benzyl ether.

One final series of experiments should be mentioned in connection with the work in this section. The explanations proposed for the non-equivalence of the methylene protons of these ethers depends on the tacit assumption that the part of the molecule containing the methylene protons comes close enough to the asymmetric center to have a preferred conformation. In order to investigate explicitly the effect of proximity to the asymmetric center on magnetic non-equivalence, we have prepared the compounds in Table IX. The non-equivalence of the methyl groups of the isopropyl group of each compound is reported in several solvents. It should be noted that the non-equivalence does not decrease monotonically, but rather decreases, increases and then falls to zero as the number of bonds between the isopropyl group and the asymmetric center increases. The simplest interpretation of these data is that cyclic conformations of the type indicated schematically below are populated to a measurable extent for the compounds containing isopropyl groups four and five bonds removed from the center of asymmetry.



In these cases, the difference in shielding at the isopropyl methyl groups is probably due to the ring current of the phenyl ring on the asymmetric center.

In conclusion, the preceding discussions enable us to draw several conclusions concerning the origin of the non-equivalence of the methylene protons of the ethers studied. These conclusions must be considered tentative pending further investigations.

The principal factor determining the chemical shift between the methylene protons in the benzyl ethers appears to be the orientation of the magnetically anisotropic phenyl group with respect to the methylene group. Conformations of the ether which are responsible for the methylene non-equivalence are not those which would be predicted to be favored on the basis of steric arguments.

The solvent dependence of ethers containing polarizable groups on both sides of the oxygen atom is suggested to be a consequence of dispersion and induction interactions between these groups. These forces have the effect of changing the preferred conformations of the molecule from those determined primarily by steric factors, in low dielectric constants solvents, to others determined primarily by these London interactions. Similar solvent dependence should probably be

Table IX

Dependence of Isopropyl Group

Non-equivalence on Proximity to the Asymmetric Center

Compound	Solvent			
	Acetone	Benzene	Carbon tetrachloride	Pyridine
$\phi CH(CH_3)CH(CH_3)_2$	11.7 cps.	8.0	10.9	8.9
$\phi CH(CH_3)OCH(CH_3)_2$	5.8	0.8	4.0	3.0
$\phi CH(CH_3)OCH_2CH(CH_3)_2$	0.0	0.5	0.3	0.0
$\phi CH(CH_3)OCH_2CH_2CH(CH_3)_2$	2.2	1.8	2.5	1.8
$\phi CH(CH_3)OCH_2CH_2OCH(CH_3)_2$	0.0	0.8	0.0	0.0
$\phi CH(CH_3)OCH_2CH_2OCH_2CH(CH_3)_2$	0.0	0.0	0.0	0.0

observed for compounds containing other polarizable groups in the asymmetric center.

The magnetic anisotropy of the benzene ring nearer the methylene protons accounts for approximately 6-8 cps. of the 11 cps. observed for the magnetic non-equivalence of the methylene protons, in benzene solution. Of the remainder, anisotropy associated with solvent molecules probably gives rise to another 0-2 cps. This latter figure may be larger in ethers in which the steric requirements around the methylene group are very severe (as in 1-phenylethyl neopentyl ether). Although no evidence was found in this study for specific solvent-solute interactions, these may be important in determining other types of non-equivalence.

Calculations of shielding differences based on recent values for the anisotropy of the carbon-carbon single bond indicated that this anisotropy is sufficiently large to be worthy of consideration in other molecules. No evidence for the incursion of this factor could be found in these ethers.

Finally, the small solvent dependence of ethers containing only alkyl groups in the asymmetric center suggests that reaction field effects are relatively unimportant in these ethers.

EXPERIMENTAL

Boiling points and melting points are uncorrected; melting points were determined with a Hershberg melting-point apparatus. Vapor chromatograms were obtained using Perkin-Elmer Vapor Fractometers Models 154-C and 800. Infrared spectra were determined with a Perkin-Elmer Model 237 double-beam grating spectrometer, using an eight-minute scan. Elementary analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Nuclear magnetic resonance spectra were obtained at 60 Mcps., using a Varian Associates Model A-60 spectrometer for the bulk of the room temperature spectra, and a Varian Associates V-4300B spectrometer with 12-in. magnet, Superstabilizer, field homogeneity control coils, and Model V3521 integrator and base-line stabilizer for variable temperature work.

Temperature control in the probe of the latter instrument was achieved by blowing dry nitrogen gas at a selected temperature over the sample and insert through an appropriate Dewar system. The insert Dewar and insert were quartz; the rest of the system was silvered pyrex. Temperatures lower than 0° were obtained by passing the nitrogen through a 5-ft. copper coil immersed in liquid nitrogen; high temperatures, by passing the gas stream over nicrome wire heated by a Variac. Temperatures in the probe were measured by means of a copper-constantan thermocouple placed close to the sample. Temperatures could be maintained constant within a degree for 15-20 min. if several minutes were allowed for equilibration following a change of temperature. Most temperatures reported in this thesis are estimated to be accurate to ±2°.

Spectral examination of diethyl ether samples at temperatures greater than +75° was made difficult by refluxing of the solvent in the sealed sample tube, if no effort were made to heat the part of the sample tube projecting above the spinner. Spectra could be obtained at much higher temperatures if the temperature of this part of the tube was regulated at approximately +120° by means of a heating element wrapped around a piece of 20-mm. O.D. glass tubing and held in position around the sample on the end of a long glass rod. Temperature control was accomplished with a Variac, and temperatures were measured with a thermocouple positioned close to the tube (between the heating element and the tube). To minimize 60 cps. modulation of the field at the sample, one half of the heating wire was wrapped around its support in a clockwise spiral, and the other half (suitably insulated) then wrapped on top in a counterclockwise spiral.

Ether samples in standard 5-mm. O.D. tubes could be examined at +120° with this apparatus. Unfortunately an appreciably amount of the ether present in the sample was in the vapor phase at temperatures above +50 - +60°, and Grignard reagent concentrations were therefore uncertain at these higher temperatures.

Measurement of line positions was accomplished by the usual audio-sideband method using a Hewlett-Packard Model 200AB audio-oscillator and Model 521-C frequency counter, when accurate measurements were required. For the majority of spectra run in diethyl ether however, it was found more convenient to use the triplet resonance of the upfield ^{13}C satellite of the solvent methyl protons to calibrate the chart sweep rate. The vicinal coupling constant in diethyl ether is 6.96 cps. (33). This

signal occurs conveniently 10-50 cps. downfield from the α-methylene resonance of the organometallic compounds. In addition, comparison of the intensity of the ^{13}C satellite resonance with that of the organometallic provides a direct measure of the concentration of the latter, because the concentration of naturally abundant $^{13}CH_3CH_2OCH_2CH_3$ in diethyl ether is known to be 2.2%. Comparison of the linewidth of the ^{13}C satellite resonances with that of the organometallic compound furnishes a simple if crude method of estimating the relative importance of exchange broadening and other less interesting broadening effects such as viscosity broadening and broadening due to field inhomogeneity.

Instrument settings for these spectra were unexceptional, except that a high r.f. power level and a broad filter bandwidth were necessary for satisfactory signal to noise ratios, due to low concentrations of organometallic in solution. Consequently, in some dilute samples there was evidence of minor saturation, but ordinarily this factor was not important in determining line shapes. Spinning noise was the principal noise source at low temperatures, where the unfortunate tendency of sample tubes to warp slightly during centrifugation became very objectionable.

Magnesium used in these Grignard reagent preparations was in the form of turnings from a bar of resublimed metal. Use of ordinary "Grignard grade" magnesium gave broad poorly resolved n.m.r. spectra, apparently due to the presence of paramagnetic impurities in solution.

Diethyl Ether. - Mallinckrodt anhydrous ether was used without further purification.

Tetrahydrofuran and diglyme were dried by distillation from sodium and stored over sodium or Linde type 5A Molecular Sieves prior to use.

Dioxane was distilled from lithium aluminum hydride and stored over sodium.

Alkyl halides used in the Grignard reagent preparations were commercially available, with the exceptions of those specifically mentioned below. They were used without further purification.

Preparation of Grignard Reagents. - All Grignard reagents examined by n.m.r. spectroscopy were prepared directly in n.m.r. tubes, following the same general procedure. To a clean, dry n.m.r. tube containing approximately 50 mg. of magnesium turnings was added 0.1 ml. of solvent and 0.1 ml. of alkyl halide by means of a 0.5 ml. syringe. Reaction was initiated by punching the magnesium with a sharpened tantalum rod. As soon as reaction was underway, 0.4 ml. more solvent was added and the tube temporarily capped. When the initial vigorous reaction had subsided, the neck of the n.m.r. tube was cleaned with a pipe-cleaner and the tube sealed to give a strong rounded end. The tube was then placed in a steam bath and heated at 100° for 6-10 hrs. with occasional shaking. The actual heating time did not appear to be critical, but at least 4 hrs. heating was required for high yields of Grignard reagent. There was no evidence of decomposition of the Grignard reagents at this temperature.

After heating, the tube was cooled and centrifuged for 10-120 min. at 1600 RPM using an International Equipment Co. Size 2 centrifuge with a type 267 head. The centrifuge buckets were packed with towels to accommodate the n.m.r. tube. Centrifugation was continued until the solution was completely free of visible magnesium chips and suspended solids. The length of time required depended on the nature and quantity

of solids present in the tube and on the solvent. The tube was positioned in the centrifuge so that the solids would be centrifuged into the upper end of the tube; spectra were obtained after centrifugation by decanting the clear solution away from the packed solids into the bottom end of the tube, and proceeding in the usual manner.

Grignard reagent solutions prepared in this manner in ether solution were perfectly colorless with approximately the same viscosity as water. The quantity of solids produced during the preparation depended primarily on the type of halide used: bromides frequently produced no solids at all; chlorides often gave small quantities of a white flocculent precipitate.

Grignard reagent solutions prepared in tetrahydrofuran were occasionally pale yellow after heating, and showed a tendency to precipitate larger amounts of solids than the corresponding ether solutions. Occasionally, a tetrahydrofuran solution of an alkylmagnesium chloride would crystallize completely; sufficient sample for n.m.r. examination could usually be recovered from the solid by centrifuging the liquid away from the solid. The signal intensity in such samples was usually slightly less than that of the same solutions before crystallization.

Tetrahydrofuran solutions occasionally gave broad spectra immediately after their preparation; resolution always improved after the sample had aged for several days. This behavior may have been a result of small concentrations of a long-lived radical species in solution.

Solutions prepared in diglyme had approximately the same characteristics as those prepared in tetrahydrofuran, except that the viscosity of the final diglyme solution was significantly greater.

No particular effort was made to dry the n.m.r. tube or the magnesium used in these studies, nor was an effort made to carry out the reactions under an inert atmosphere. The fact that little or no difficulty was encountered in initiating most of these reactions suggests that the solutions were not seriously wet. On the short periods in which the n.m.r. tubes were open to the atmosphere (as during the cleaning and sealing operations) the Grignard reagent solutions were probably adequately protected by the 10 cm. column of ether vapor above the solution in the n.m.r. tube.

Dialkylmagnesium solutions were prepared from the corresponding Grignard reagents by opening the n.m.r. tube, adding 100 μl. of dry dioxane and then capping and shaking the tube. The dioxane addition resulted in immediate production of a voluminous white precipitate in such quantity that the sample frequently became almost solid. The precipitations were mildly exothermic processes.

The neck of the tube was cleaned with pipe-cleaner and sealed in the usual manner. After sealing, the solution was allowed to stand in contact with the precipitate for 10-12 hrs. with frequent shaking, and then centrifuged in the manner described previously. Three to four hrs. centrifugation at 1600 RPM were frequently required to compact completely the voluminous precipitate of magnesium halide dioxanate. The volume of the compacted precipitate was usually approximately one-third that of the original Grignard reagent solution. This precipitate was usually removed from dialkylmagnesium samples to be examined at high temperature by cutting off the part of the tube containing the precipitate and immediately sealing the tube again.

Grignard reagents and dialkylmagnesium compounds containing a $-\underline{CH_2}-Mg$ group were identified by the characteristic chemical shift and spin-coupling patterns of their α protons. The resonances of protons geminal to a strongly electropositive metal occur at significantly higher field than those of any of the other compounds likely to occur in the solution; these protons could consequently be recognized and examined without difficulty. The α-proton resonances of the secondary Grignard reagents were usually more complicated by spin-coupling and of lower intensity than those of the primary Grignard reagents, and were frequently difficult to find. These Grignard reagents were characterized by addition of a slight excess of water to the sample tube followed by centrifugation to remove the precipitated magnesium salts. Comparison of the spectrum of the organometallic solution and that of the hydrolyzed solution with the spectra of solutions in the same solvent of the starting halide and of the hydrocarbon expected from hydrolysis (when available) usually allowed the resonances due to Grignard reagent to be identified without difficulty.

Yields of Grignard reagent in diethyl ether solution were estimated to be 70-95% by comparison with the ^{13}C satellites of solvent, based on starting halide.

Diisopropylmagnesium was prepared in synthetic quantity following standard procedures (59) by addition of 66 g. (0.75 mole) of dry dioxane to a Grignard solution prepared from 92 g. (0.75 mole) of 2-bromopropane and 18 g. (0.75 mole) of magnesium in 300 ml. of ether in a 1-l. three-necked round-bottomed flask equipped with mechanical stirrer, condenser and pressure equalized dropping funnel. The precipitated magnesium bromide dioxanate was not separated from the dialkylmagnesium solution.

2-Phenyl-3-methyl-1-butanol. - To the diisopropylmagnesium solution prepared above was added 60 g. (0.50 mole) of styrene oxide at such a rate as to maintain gentle refluxing. The reaction mixture was stirred for 4 hrs. at room temperature, refluxed for 1 hr., and hydrolyzed with saturated aqueous ammonium chloride solution to the point at which the solids conglomerated on the sides of the flask. The ether layer was decanted from the salts and dried over calcium sulfate. Removal of the ether on a rotary evaporator and distillation of the residue through a 20-cm. wire-spiral column yielded 53 g. of product, b.p. 84-87° (2 mm.) lit. (60) b.p. 93° (4 mm.); purity of the product was estimated to be 90-95% from the n.m.r. spectrum.

2-Phenyl-3-methylbutyl chloride was prepared by addition of 50 ml. of thionyl chloride to a solution of 25 ml. of 2-phenyl-3-methyl-1-butanol and 50 ml. of dimethylformamide in a 200-ml. Erlenmeyer flask immersed in an ice-bath. The temperature of the solution was maintained at 15 ± 5° during the addition. The solution was allowed to stand at room temperature for 6 hrs. after addition of the thionyl chloride, then hydrolyzed by pouring into 200 ml. of cold water. The organic layer was separated and the aqueous layer extracted twice with 50-ml. portions of ether. The combined organic layer was dried over calcium chloride, then distilled twice through a 20-cm. wire-spiral column at reduced pressure to yield 12 g. (approximately 45%) of product, b.p. 67-74° (0.8 mm.).

Anal. Calcd. for $C_{11}H_{15}Cl$: C, 72.32; H, 8.28; Cl, 19.41. Found: C, 72.55; H, 8.26; Cl, 19.18.

2-Phenyl-3-methylbutylmagnesium chloride could be prepared from the chloride only with difficulty. The procedure finally settled upon

was to add 0.1 ml. of the chloride and 0.1 ml. of ether to magnesium turnings in an n.m.r. tube. The magnesium turnings were then pulverized with a nicrome wire. Onto this mixture was poured 0.4 ml. of ether without mixing the layers. The tube was sealed and heated in the usual manner; after approximately 1 hr. at 100° reaction between magnesium and the halide occurred. The remainer of the preparation was unexceptional.

1,3-Dibromo-2,2-dimethylpropane. - The procedure used was a modification of that of Schurink (61). In a 500-ml. round-bottomed three-necked flask equipped with a pressure-equalized dropping funnel and air-cooled condenser was placed 183 g. (0.92 mole) of 2,2-dimethyl-1,3-propanediol. The flask was heated on the steam bath and 500 g. of freshly opened phosphorus tribromide was added over the course of 2 hrs. The steam bath was exchanged for an oil bath and the temperature increased to 160°. The temperature was maintained at this level for 24 hrs. The heterogeneous mixture resulting was then cooled and poured into 1 l. of water. The lower layer was separated and dried over calcium sulfate. The n.m.r. spectrum indicated that this material was approximately 70% the desired bromide. The yield was 200 g., and product was used without further purification.

3,3-Dimethylcyclobutanecarboxylic acid was prepared following the procedure of Campbell and Rydon (62), substituting the crude 1,3-dibromo-2,2-dimethylpropane prepared above for the 1,3-diiodo-2,2-dimethylpropane used by these workers. The yield of acid was 22 g., b.p. 75-103° (12 mm.); lit. (62) b.p. 105-106° (15 mm.).

Silver 3,3-dimethylcyclobutanecarboxylate was prepared from 3,3-dimethylcyclobutanecarboxylic acid following the standard procedure of

Cason and Way (63). The silver salt was air dried to a powder at room temperature, and dried at 0.5 mm. for four days prior to its use in the brominative decarboxylation.

3,3-Dimethylcyclobutyl Bromide from Silver 3,3-Dimethylcyclobutanecarboxylate. - The reaction conditions used were modeled on those in ref. (63), except that the solution temperature was maintained at 0° rather than at -20°. The flask used for the reaction was dried by distilling 50 ml. of carbon tetrachloride from it immediately before use. Bromine and carbon tetrachloride were dried by distillation from phosphorus pentoxide.

The silver salt (38.9 g., 0.17 mole) was added over the course of 1 hr. to 250 ml. of carbon tetrachloride and 28.9 g. (0.18 mole) of bromine in a 500-ml. three-necked round-bottomed flask equipped with mechanical stirrer and thermometer and immersed in a Dry-Ice-acetone bath. The salt was added through a piece of Gooch tubing connecting one inlet of the reaction flask directly to the Erlenmeyer flask in which the salt had been dried. No carbon dioxide evolution was observed until the solution had been warmed briefly to +20°; after the reaction had started, the solution was cooled to 0° and the remainder of the silver salt added. When gas evolution had ceased, the reaction mixture was allowed to stand overnight and then filtered, washed once with aqueous sodium bisulfite, once with 2 N potassium hydroxide, and once with water. The organic layer was dried over calcium sulfate, and the carbon tetrachloride removed through a 10 cm. glass helix-packed column. The bromide was distilled under slightly reduced pressure through a 30-cm. Vigreux column. The product (12 g., 45%) had b.p. 132° by the capillary b.p.

method. The purity of the product was approximately 95% as estimated by v.p.c. (column K, 110°). N.m.r. and infrared spectra were consistent with desired structure.

Anal. Calcd. for $C_6H_{11}Br$: C, 44.19; H, 6.80; Br, 49.01. Found: C, 44.13; H, 5.94; Br, 48.80.

2-Methyl-2-carboethoxycyclopentanone from 2-Carboethoxycyclopentanone. - The procedure used followed that of Case and Reid (64). To 17.5 g. (0.75 mole) of sodium hydride (as a 50% suspension in mineral oil) in 400 ml. of reagent benzene in a 1-l. three-necked round-bottomed flask equipped with a 250-ml. dropping funnel, condenser and mechanical stirrer, 156 g. (0.65 mole) of 2-carboethoxycyclopentanone was added with stirring over 1 hr. (The 2-carboethoxycyclopentanone used contained a large amount of 2-carbomethoxycyclopentanone as impurity.) To the sodium salt thus formed, 110 g. (0.75 mole) of methyl iodide was added. The mixture was stirred and refluxed for 24 hrs. Precipitated sodium iodide was then filtered from the solution, benzene removed on a rotary evaporator and the residue distilled to give 69 g. (62%) of product. The crude material had b.p. 104-114° (27 mm.); lit. (64) b.p. 106-107° (17 mm.) corr. and was used without further purification.

Sulfuric acid-d_2 in deuterium oxide was prepared by bulb-to-bulb distillation of 4 ml. of sulfur trioxide (Baker and Adamson "Sulfam B") into 25 ml. of deuterium oxide on a vacuum line (65).

2-Methylcyclopentanone-2-d from 2-Methyl-2-carboethoxycyclopentanone. - The procedure used was adapted from that of ref. (64) for conversion of 2-ethyl-2-carboethoxycyclopentanone to 2-ethylcyclopentanone. To the sulfuric acid-d_2/deuterium oxide solution prepared as described above,

in a 100-ml. round-bottomed flask with condenser, was added 15 ml. of 2-carboethoxycyclopentanone, and the mixture refluxed for 4 hrs. The heterogeneous solution was cooled and extracted three times with 50 ml. portions of ether. The acid layer was refluxed again with 15 ml. of ester, and this mixture worked up in the same way. The combined ether layers were shaken with solid anhydrous sodium carbonate for 45 min., washed with 2 ml. of deuterium oxide saturated with sodium carbonate, then dried over calcium sulfate. The ether was removed and the residue distilled to give 16.5 g. of ketone (approximately 90% pure) b.p. 110-135°; lit. (66) b.p. 139.5°. The n.m.r. spectrum of this compound showed one type of methyl group with the triplet structure expected for a $CD-CH_3$ moiety. The infrared spectrum had the expected absorption at 1740 $cm.^{-1}$ and weak absorption around 2140 $cm.^{-1}$.

The 2,4-dinitrophenylhydrazone of the ketone prepared in a trial of this procedure using sulfuric acid/water had m.p. 158.5-159.0° after five recrystallizations from ethanol/ethyl acetate; lit. (67) m.p. 159.0-159.4°.

2-Methylcyclopentanol-2-d was prepared from 16.5 g. of 2-methylcyclopentanone-2-d by reduction with 5 g. of lithium aluminum hydride in 100 ml. of ether in the usual fashion. The infrared spectrum of the crude product obtained after hydrolysis, drying and removal of the ether indicated that no ketone remained. The product was not purified further.

2-Methylcyclopentyl Chloride-2-d from 2-Methylcyclopentanol-2-d. - To a solution of dimethylformamide (40 ml.) and 20 ml. of 2-methylcyclopentanol-2-d in a 250 ml. Erlenmeyer flask in an ice bath was added 20 ml. of thionyl chloride. The reaction mixture was allowed to stand in ice

for 20 min., then warmed to room temperature. The reaction mixture turned black on warming. The solution was placed in the refrigerator for 2 hrs., then poured onto approximately 1 kg. of cracked ice. The ice was allowed to melt, and the aqueous layer extracted three times with 100 ml. portions of ether. The combined ether layer was washed once with 100 ml. of water, then neutralized by washing with aqueous sodium bicarbonate solution. The ether layer was dried over calcium chloride, and the ether removed on a rotary evaporator. The residue was flash distilled to separate product from tar, then distilled again through a 30-cm. wire-spiral column (some decomposition). The product, b.p. 122-126° was still impure and final purification was effected using an Aerograph "Autoprep" preparative v.p.c. equipped with a 20-ft. silicone-oil column operating at 110°. Recovery was poor (approximately 1 g.) but the material so obtained consisted of only one component by analytical v.p.c., and had n.m.r. and infrared spectra consistent with the desired product. The material collected from the v.p.c. was the stereoisomer present originally in greater quantity (probably the isomer with methyl group and chlorine atom trans).

Analyses of n.m.r. spectra were performed using a standard iterative program (69). Measured line positions (Obs.), calculated line positions (Calc.) and intensities (Int.) are given below for 3,3-dimethylbutyl chloride in carbon tetrachloride solution at +33° (Table I) and for bis-(3,3-dimethylbutyl)-magnesium in diethyl ether solution at +33° (Table II). The A and B parts of the spectra are mirror images; only one half is given. The solution obtained for 3,3-dimethylbutyl chloride [and by inference for bis-(3,3-dimethylbutyl)-magnesium] is not unique -- an

equally close fit between observed and calculated spectra could be obtained using all positive signs for the coupling constants. In the latter solution the magnitudes J_A and J_B were different than those reported here; the magnitudes of the vicinal coupling constants were the same.

Table I

Observed and Calculated Spectra for 3,3-Dimethylbutyl Chloride

Input Parameters

ν_1	100.19	J_{12}	-13.89
ν_2	100.19	J_{13}	5.45
ν_3	203.38	J_{14}	11.19
ν_4	203.38	J_{23}	11.19
		J_{24}	5.45
		J_{34}	-10.69

Line	Obs.	Calc.	Int.
1	-	74.63	0.017
2	91.3	91.21	1.682
3	91.7	91.85	1.711
4	95.3	95.23	0.466
5	98.4	98.43	1.436
6	99.2	99.01	1.916
7	99.9	99.97	1.953
8	101.8	101.80	1.534
9	105.0	105.00	0.564
10	108.1	107.85	2.318
11	108.1	108.36	2.355
12	-	124.42	0.047

Table II

Observed and Calculated Spectra for

Bis-(3,3-dimethylbutyl)-magnesium

Input Parameters

ν_1	22.10	J_{12}	-15.98
ν_2	22.10	J_{13}	4.16
ν_3	150.54	J_{14}	14.01
ν_4	150.54	J_{23}	14.01
		J_{24}	4.16
		J_{34}	-14.81

Line	Obs.	Calc.	Int.
1	-	-10.03	0.031
2	12.6	12.38	1.720
3	12.6	12.90	1.740
4	16.4	16.37	0.806
5	17.6	17.54	1.042
6	20.5	20.60	1.895
7	22.4	22.33	1.949
8	26.3	26.29	1.194
9	27.4	27.46	0.958
10	30.7	30.55	2.280
11	30.7	30.91	2.299
12	-	52.96	0.086

Analyses of the ABX spectra of the 2-phenyl-3-methylbutylmagnesium derivatives were considerably more uncertain than those for the AA'XX' systems, because the low-intensity outer lines of the AB part of the spectrum frequently could not be distinguished above the noise level, and because the X part of the spectrum could not be analyzed at all. The results of calculations for 2-phenyl-3-methylbutylmagnesium chloride in diethyl ether at -14° and in tetrahydrofuran at +33°, and for bis-(2-phenyl-3-methylbutyl)-magnesium in diethyl ether at +33° are given in Table III. The chemical shift between the AB and X protons was assumed to be approximately 150 cps. The error in the values reported in Table III is estimated to be ±0.5 cps.

Calculation of Activation Parameters from Variable Temperature Spectra. - The theory supporting these calculations has been discussed previously.

Separations in the spectrum of bis-(3,3-dimethylbutyl)-magnesium and 3,3-dimethylbutylmagnesium chloride were determined using the separation between the 1,2 and 3,4 transitions as a standard. These separations were determined separately by standard audio-side-band methods, using internal benzene as the reference signal. This separation was determined at three temperatures for each compound. For bis-(3,3-dimethylbutyl)-magnesium the values obtained for the separation were (the numbers in parentheses refer to the number of separate readings at that temperature): T = +33°, S = 18.0 ± 0.2 cps. (8 values); T = +73°, S = 18.1 ± 0.3 cps. (8 values); T = +101° to +103°, S = 18.0 ± 0.2 cps. (15 values). For 3,3-dimethylbutylmagnesium chloride, the corresponding values were: T = +33°, S = 18.2 ± 0.1 cps. (12 values); T = -41° to -45°, S = 18.3 ± 0.4 cps. (6 values); T = -51° to -55°, S = 18.4 ± 0.3 cps. (12 values).

Table III

Observed and Calculated Spectra for the α-Methylene Protons of 2-Phenyl-3-methylbutylmagnesium X

	X = Cl; Diethyl Ether			X = Cl; Tetrahydrofuran			X = R; Diethyl Ether		
Input Parameters									
ν_1	50.0			50.2			50.4		
ν_2	62.9			59.4			64.6		
ν_3	200.0			200.0			200.0		
J_{12}	-12.2			-12.2			-12.2		
J_{13}	10.3			9.7			10.2		
J_{23}	4.3			5.6			3.2		
Line	Obs.	Calc.	Int.	Obs.	Calc.	Int.	Obs.	Calc.	Int.
1	36.5	36.5	0.338	36.2	36.4	0.242	36.8	37.1	0.396
2	-	46.0	0.254	-	45.4	0.157	-	46.5	0.281
3	48.7	48.7	1.511	48.4	48.5	1.634	49.2	49.3	1.474
4	56.9	56.7	1.546	53.6	53.2	1.658	59.0	58.7	1.842
5	58.5	58.2	1.872	57.8	57.6	1.964	59.0	58.8	1.514
6	61.5	61.7	1.843	59.2	59.5	1.944	62.6	62.8	1.808
7	69.1	68.9	0.386	-	65.4	0.250	71.4	71.0	0.432
8	-	73.9	0.231	-	71.6	0.145	-	74.9	0.252

The separation measured in the spectrum to obtain the plots in Fig. 17 was the estimated separation between the mean value of the 9 and 10 transitions, and the 11 and 12 transitions. The assumption was made that the separation between the 1,2 and 3,4 transitions was constant over the temperature range and had the value 18.0 cps. for bis-(3,3-dimethylbutyl)-magnesium and 18.2 cps. for 3,3-dimethylbutylmagnesium chloride.

The value for the reciprocal of the pre-exchange lifetime τ was obtained at each temperature using the formula

$$\frac{1}{\tau} = \left[\frac{4\pi^2(\delta^2 - \Delta_e^2)}{8}\right]^{\frac{1}{2}}$$

where δ is the limiting low temperature separation between the 9,10 and 11,12 transitions, and Δ_e is this separation at each temperature T. The units of δ and Δ_e are cps. The values of $1/\tau$ obtained are listed in Table IV. The value of δ used for bis-(3,3-dimethylbutyl)-magnesium was 10.5 cps.; for 3,3-dimethylbutylmagnesium chloride it was 11.8 cps.

To obtain the activation energies for the 2-phenyl-3-methylbutyl-magnesium derivatives, the spectra were analyzed at each temperature to obtain $\nu_A - \nu_B$. In order to analyze the spectra, it was necessary to assume a value for J_{AB}; in each case this coupling constant was given the value -12.2 cps. With this assumption, the complete spectrum could be constructed by measuring the positions of the four central lines and then adding or subtracting (depending on whether the line considered was an A or a B transition) J_{AB} to obtain the approximate values of the

Table IV

Separations and Temperatures Used in Obtaining the Dependence of $(1/\tau)$ on $1/T$ for Bis-(3,3-dimethylbutyl)-magnesium

T°K	$1/T \times 10^3$	∇_e	$\delta^2 - \nabla_e^2$	$(1/\tau)$	log $(1/\tau)$
354	2.82	0.0	110.3	23.32	1.36
348	2.87	4.9	86.2	20.60	1.31
339	2.95	7.8	49.3	15.58	1.91
334	2.99	8.8	33.0	12.76	1.10
322	3.11	9.4	20.6	10.06	1.00
302	3.31	9.8	10.7	7.34	0.87
301	3.32	9.8	10.7	7.34	0.87
268	3.73	10.3	3.13	3.82	0.58
253	3.95	10.4	2.09	3.20	0.50
208	4.81	10.5	0.0	0.00	-

Table V

Separations and Temperatures Used in Obtaining the Dependence of $(1/\tau)$ on $1/T$ for 3,3-Dimethylbutylmagnesium Chloride

T°K	$1/T \times 10^3$	∇_e	$\delta^2 - \nabla_e^2$	$(1/\tau)$	log $(1/\tau)$
243	4.12	0.00	139.2	26.2	1.42
232	4.31	8.87	60.6	17.2	1.23
223	4.48	10.4	31.1	12.4	1.09
213	4.69	10.8	22.6	10.6	1.02
201	4.96	11.8	0.0	0.0	-

weak transitions. Spectra completed in this way could then be analyzed to obtain $\nu_A - \nu_B$. The dependence of $1/\tau$ on $1/T$ was obtained by using these values of $\nu_A - \nu_B$ directedly in the treatment of Gutowsky and Holm. The data are given in Table VI: Note that τ in this table has the same meaning as in Table IV: i.e. this τ is twice the value of the used by Gutowsky. The value of $1/T_2$ in this treatment was taken as 0.5 cps. Here, all frequencies are in units of cps., and $1/\tau$ has the units $sec.^{-1}$.

Table VI

Separations and Temperatures Used in Obtaining the Dependence of $1/\tau$ on $1/T$ for 2-Phenyl-3-methylbutylmagnesium Chloride

a) Diethyl Ether Solution

T°K	$1/T \times 10^3$	$\nu_A - \nu_B$	$(1/\tau)$	log $(1/\tau)$
259		13.1	-	-
269	3.72	12.8	3.33	0.52
279	3.58	12.8	3.33	0.52
305	3.29	12.0	8.23	0.92
305	3.29	11.7	9.49	1.00
323	3.10	7.7	19.4	1.29
330	3.03	0.0	24.3	1.38

b) Tetrahydrofuran Solution

T°K	$1/T \times 10^3$	$\nu_A - \nu_B$	$(1/\tau)$	log $(1/\tau)$
339		10.0	-	-
346	2.89	9.7	2.82	0.45
360	2.78	9.8	2.51	0.40
365	2.74	9.1	5.65	0.75
364	2.74	8.4	7.85	0.89
370	2.70	6.9	11.6	1.06
373	2.68	6.0	13.5	1.13
379	2.64	0.0	17.3	1.24

Part II.

Benzyl isobutyl ether was prepared in a 250-ml. round-bottomed flask equipped with a reflux condenser, by refluxing 14.8 g. (0.2 mole) of isobutyl alcohol and 18.9 g. (0.15 mole) of benzyl chloride with an excess of potassium hydroxide pellets for 24 hrs. The organic layer was separated, washed twice with 500-ml. portions of water and dried over calcium sulfate. Distillation through a 30-cm. wire-spiral packed column yielded approximately 10 g. of product, b.p. 75-80° (3 mm.). The product was identified by its n.m.r. spectrum. The n.m.r. spectrum of this ether (and of the other ethers described in this section) was easily recognized, because of the close similarity of its spin-spin splitting patterns to those of the starting materials.

Benzyl Isopropylmethylcarbinyl Ether. - Commercial silver oxide (18.9 g., 0.15 mole), and a Teflon-covered stirring bar were placed in a 100-ml. round-bottomed flask equipped with a reflux condenser. To the flask was added 18.9 g. (0.15 mole) of benzyl bromide and 12.0 g. (0.14 mole) of 3-methyl-2-butanol, and the resulting slurry refluxed with stirring for 24 hrs. The mixture was cooled, and the inorganic solids removed by filtration. The organic layer was washed once with acidic 5% aqueous ferrous sulfate solution, once with water, and then dried over calcium sulfate. Distillation through a 30-cm. wire-spiral packed column yielded approximately 10 g. of product, b.p. 85-87° (6 mm.). The product was identified by its n.m.r. spectrum.

3,3-Dimethyl-2-butanol was prepared by reduction of 20.2 g. (0.2 mole) of t-butyl methyl ketone with 2.27 g. (0.6 mole) of lithium aluminum hydride in refluxing ether. Hydrolysis of the reaction mixture

with saturated aqueous ammonium chloride solution, removal of water with calcium sulfate, and distillation through a 30-cm. wire-spiral packed column yielded 12 g. of product, b.p. 110-111°. The product had the expected n.m.r. and infrared spectra, and was not characterized further.

Benzyl t-Butylmethylcarbinyl Ether. - In a 500-ml. round-bottomed flask equipped with a reflux condenser and a Teflon-covered stirring bar were mixed 12 g. (0.11 mole) of 3,3-dimethyl-1-butanol, 2.6 g. of sodium hydride (as a 50% dispersion in mineral oil) and 250 ml. of anhydrous ether. The slurry was refluxed with stirring for 8 hrs. to form the sodium alkoxide. Benzyl bromide (18.8 g., 0.11 mole) was then added and refluxing continued for 12 hrs. The reaction mixture was cautiously washed with two 100-ml. portions of water, dried over calcium sulfate and distilled to yield approximately 7 g. of product. The purest fraction had b.p. 90-92° (7 mm.), and was characterized by its n.m.r. spectrum.

Anal. Calcd. for $C_{13}H_{20}O$: C, 80.20; H, 10.48. Found: C, 80.21; H, 9.92.

Cyclohexylmethylcarbinol was prepared by addition of 80 g. of acetaldehyde to the Grignard reagent from 30 g. of magnesium turnings, 150 g. of cyclohexyl bromide, and 500 ml. of ether, in the usual apparatus. Hydrolysis of the reaction mixture with saturated aqueous ammonium chloride solution, followed by removal of water with calcium sulfate and distillation yielded a large quantity of colorless liquid b.p. 65-70° (9 mm.). The infrared spectrum of this material showed very strong carbonyl absorption at 1700 $cm.^{-1}$ and weak hydroxyl absorption.

Addition of several small pieces of sodium to the material at room temperature resulted in a violent polymerization of the bulk of the liquid. The polymer was allowed to stand for 12 hrs., then removed by filtration, yielding essentially pure cyclohexylmethylcarbinol, characterized by its strong infrared absorption at 3350 cm.$^{-1}$, by its n.m.r. spectrum, and by its b.p. 77-83° (11 mm.), lit. (91) b.p. 87° (11 mm.). The carbonyl absorption in the distilled material was almost unnoticeable.

Benzyl Cyclohexylmethylcarbinyl Ether. - Silver oxide (16 g., 0.07 mole), benzyl bromide (10 g., 0.057 mole) and cyclohexylmethylcarbinol (8 g., 0.057 mole) were heated together with stirring for 48 hrs. at approximately 150°. At the end of this time, the slurry was cooled, taken up in five times its own volume of ether, filtered, and distilled yielding approximately 2 g. of product, b.p. 126-133° (4 mm.), contaminated with approximately 20% of benzyl alcohol. The product was characterized by its n.m.r. spectrum.

Anal. Calcd. for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.88; H, 9.64.

Benzyl Phenylmethylcarbinyl Ether. - Benzyl alcohol and 1-phenylethyl bromide (mole ratio 1:1) were heated in an Erlenmayer flask on a steam bath for 6 hrs. The solution was cooled, the inorganic salts removed by filtration, and the organic filtrate washed with water and dried over excess powdered calcium chloride. The organic layer was then distilled to yield 45% of the desired ether, b.p. 123-124° (0.3 mm.). The infrared spectrum showed a strong band at 1100 cm.$^{-1}$ and no absorption in the 3500 cm.$^{-1}$ region. The n.m.r. spectrum of the compound was consistent with the assigned structure. The high boiling point of

this material prevented its purification by preparative v.p.c.; the analytical sample used was therefore obtained by distillation.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.78; H, 7.64.

Carboethoxymethylcarbinyl Benzyl Ether. - Sodium benzylate was prepared by the reaction of 22 g. (0.2 mole) of benzyl alcohol with 5.6 g. (0.22 mole) of sodium hydride (50% suspension in mineral oil) in 300 ml. of ether in a 1-l. three-necked round-bottomed flask equipped with reflux condenser, mechanical stirrer, dropping funnel and heating mantle. When formation of the alkoxide was complete (as judged by evolution of hydrogen) 36.2 g. of ethyl α-bromopropionate was added. The mixture was stirred overnight, then filtered to remove inorganic salts. The ether was removed on a rotary evaporator and the residue distilled to yield approximately 5 g. of product, b.p. 88-92° (2 mm.). The n.m.r. spectrum of the compound was consistent with the assigned structure.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.06; H, 7.74.

1-Phenylethyl isopropyl ether was prepared by refluxing a mixture of 20 ml. of 1-phenylethyl bromide and 60 ml. of isopropanol for 48 hrs. in a 250-ml. round-bottomed flask equipped with reflux condenser and heating mantle. The resulting turbid solution was cooled, neutralized with sodium carbonate, washed with two 500-ml. portions of water and dried over calcium sulfate. Distillation at reduced pressure yielded approximately 25 ml. of product, b.p. 94-97° (35 mm.), whose n.m.r. spectrum was consistent with the assigned structure.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.40; H, 9.83. Found: C, 80.03; H, 9.97.

1-Phenylethyl 2-methylpropyl ether was prepared by an identical procedure, starting with 93 ml. of 2-methylpropanol and 45 g. of 1-phenylethyl bromide. The product had b.p. 58-63° (3 mm.). Its n.m.r. spectrum was consistent with the assigned structure.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.45; H, 9.87.

1-Phenylethyl 3-methylbutyl ether was also prepared using this procedure, starting with 36.6 ml. of 3-methylbutanol and 41 g. of 1-phenylethyl bromide. The product had b.p. 106-108° (2 mm.), and the n.m.r. spectrum expected for the assigned structure.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.62; H, 9.97.

2-Isopropoxyethanol was prepared by refluxing 200 ml. of ethylene glycol and 100 ml. of isopropyl bromide over 60 g. of sodium carbonate for 48 hrs. in a 500-ml. flask fitted with a reflux condenser. The mixture was cooled, and the inorganic salts removed by filtration. Distillation through a 30-cm. wire-spiral packed column gave 45 ml. of product, b.p. 128-138° (wet), lit. (92) b.p. 144°. The product was not purified further, but was used immediately.

1-Isopropoxy-2-(1-phenylethoxy)-ethane. - In a 100-ml. round-bottomed flask fitted with a heating mantle were placed a Teflon-covered stirring bar, 5 ml. of 1-phenylethyl bromide and 10 ml. of 2-isopropoxyethanol, and the slurry heated to approximately 150°. Silver oxide (5 g.) was added. After an induction period of approximately 30 min., a vigorous

exothermic reaction occurred. When this had subsided, 7 g. more silver oxide and 15 ml. more 1-phenylethyl bromide were added in portions. Finally, the slurry was allowed to stir at 150° overnight. The mixture was then cooled, taken up in 25 ml. of ether, filtered, washed once with 20 ml. of 10% aqueous acidic ferrous sulfate solution, once with water, and dried over calcium sulfate. The ether was removed on a rotary evaporator and the residue fractionated through a 10-cm. Vigreux column at reduced pressure. The yield of product, b.p. 95-105° at 1 mm., was 10 ml.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.77; H, 9.73.

2-Isobutoxyethanol was prepared from 130 ml. of ethylene glycol, 80 ml. of isobutyl bromide and 50 g. of sodium carbonate as described previously for 2-isopropoxyethanol. The yield of product, b.p. 138-145° (wet), lit. (92) 154°, was 17 ml.

1-Isobutoxy-2-(1-phenylethoxy)-ethane was prepared from 17 ml. of 2-isobutoxyethanol, 12 g. of silver oxide and 20 ml. of 1-phenylethyl bromide as described above for 1-isopropoxy-2-(1-phenylethoxy)-ethane. The product was obtained in approximately 10 ml. yield, and had b.p. 100-108° (1 mm.).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.01; H, 9.81.

1-Phenylethyl neopentyl ether was prepared in approximately 30% yield from 8.8 g. (0.1 mole) of neopentyl alcohol, 20 g. (0.1 mole) of 1-phenylethyl bromide and 13 g. (0.1 mole) of silver oxide. These components were mixed in a 100-ml. round-bottomed flask. After an

initial exothermic reaction had subsided, 3 g. more silver oxide and 5 ml. more 1-phenylethyl bromide were added and the reaction mixture heated on the steam bath for 24 hrs. The mixture was cooled and the product isolated as described for 1-isopropoxy-2-(1-phenylethoxy)-ethane. The crude ether had b.p. 86-91° (16 mm.) and was contaminated with appreciable quantities of 1-phenylethyl bromide. Purification was effected by dissolving the mixture of halide and ether in diethyl ether, and allowing the solution to stand over sodium for 24 hrs. The solution was decanted from the unreacted sodium and redistilled to yield the spectral samples. The n.m.r. spectrum of this material was consistent with the assigned structure.

1-Phenylethyl ethyl ether was prepared in these laboratories by F. Kaplan.

2-Methyl-3-phenylbutane was prepared in poor yield by reaction of approximately 0.2 mole of isopropylmagnesium bromide with an equivalent amount of 1-phenylethyl bromide in ether. The reaction mixture was hydrolyzed with saturated aqueous ammonium chloride solution, and the ether layer from the hydrolysis dried and distilled in the usual manner to yield approximately 2 ml. of the desired hydrocarbon, b.p. 85-105° (18 mm.). The principal product of this reaction is 2,3-diphenylbutane, apparently arising from a metal-halogen exchange reaction between isopropyl Grignard reagent and 1-phenylethyl bromide.

1-Phenylethyl benzyl sulfide was synthesized by modification of the procedure used by Backer and Jong (93) to prepare allyl benzyl sulfide. Ethanol (100 ml.), 16 g. of sodium hydroxide and 50 g. of benzyl mercaptan were heated together for 3 hrs. in a beaker on a steam

bath. The solution was then cooled in an ice bath, and 80 g. of 1-phenylethyl bromide added. An immediate exothermic reaction occurred, accompanied by formation of a white precipitate. The mixture was allowed to warm to room temperature over 5 hrs., then poured into 500 ml. of water. The lower (organic) layer was separated and dried, yielding the sulfide in approximately 90% purity (estimated from its n.m.r. spectrum). The product did not distill at 150° and 0.5 mm., nor could it be induced to crystallize.

1-Phenylethyl benzyl sulfone was prepared by careful addition of 5.7 ml. of 30% hydrogen peroxide solution (0.05 mole of hydrogen peroxide) to an ice-cold solution of 1-phenylethyl benzyl sulfide (5.7 g., 0.025 mole) in 10 ml. of 1:1 acetic acid: acetic anhydride solvent, followed by digestion on the steam bath for 24 hrs. The product, obtained as a white crystalline solid on cooling the solution, was washed with water, filtered and air dried. The infrared spectrum displayed prominent bands at 1135 $cm.^{-1}$ and 1325 $cm.^{-1}$ characteristic of the sulfone moiety.

1-Phenylethyl p-chlorobenzyl ether and 1-p-chlorophenylethyl benzyl ether were prepared in these laboratories by John Grocki.

Table

Solvent Dependence of Chemical Shifts and Coupling Constants for 1-Phenylethyl Benzyl Ether

Solvent	Mole %	$\nu_A - \nu_B$	J_{AB}	J_{CH_3-H}	ν_A (a)	ν_B (a)	ν_C (a)	ν_{CH_3} (a)
C_6H_6	8.8	10.9 ± .7	11.8 ± .2	6.7 ± .4	259.9 ± .5	248.9 ± .5	260.2 ± .2	86.8 ± .5
C_6H_5Cl	9.9	8.2 ± .8	11.5 ± .2	6.5 ± .4	261.0 ± .6	252.8 ± .6	262.0 ± .2	83.7 ± .5
o-$C_6H_4Cl_2$	9.6	7.2 ± .8	11.3 ± .2	6.5 ± .4	260.9 ± .6	253.7 ± .6	263.6 ± .2	85.0 ± .5
$C_6H_5NO_2$	10.2	3.8 ± 1.0	11.7 ± .2	6.4 ± .4	263.5 ± 1.0	259.7 ± 1.0	270.5 ± .2	87.8 ± .5
Pyridine	9.2	6.1 ± 1.0	11.5 ± .2	6.3 ± .4	267.1 ± .6	261.0 ± .6	270.6 ± .2	87.1 ± .5
$C_6H_5NH_2$	9.4	7.8 ± .8	12.1 ± .2	6.4 ± .4	257.2 ± .6	249.4 ± .6	257.3 ± .2	81.8 ± .5
$C_6H_5NH_2$	4.3	8.4 ± .8	11.6 ± .2	6.3 ± .4	257.8 ± .6	249.4 ± .6	257.3 ± .2	80.1 ± .2
$C_6H_5NH_2$	.9	——	——	6.4 ± .4	——	——	——	80.7 ± .2
C_6H_5CN	10.0	3.8 ± 1.5	10.1 ± .2	6.5 ± .4	262.4 ± 1.2	258.6 ± 1.2	269.4 ± .2	85.9 ± .5
C_6H_5CN	5.2	——	——	6.1 ± .4	——	——	268.8 ± .2	84.4 ± .2
C_6H_{12}	10.2	10.1 ± .7	11.5 ± .2	6.3 ± .4	261.5 ± .5	251.0 ± .5	261.6 ± .2	——
C_6H_{12}	4.8	10.1 ± .7	11.7 ± .2	6.1 ± .4	261.9 ± .5	251.8 ± .5	261.8 ± .2	——
n-C_5H_{12}	10.0	10.1 ± .7	11.6 ± .2	6.2 ± .4	262.5 ± .5	252.5 ± .5	262.5 ± .2	——

Solvent	Mole %	$\nu_A - \nu_B$	J_{AB}	J_{CH_3-H}	ν_A	ν_B	ν_C	ν_{CH_3}
n-C_5H_{12}	6.0	10.1 ± .7	11.5 ± .2	6.3 ± .4	261.8 ± .5	251.7 ± .5	261.8 ± .2	——
CCl_4	9.7	10.2 ± .7	12.3 ± .2	6.6 ± .4	261.0 ± .5	250.8 ± .5	262.9 ± .2	87.2 ± .5
CCl_4	1.1	——	——	6.2 ± .4	——	——	——	83.5 ± .5
$CHCl_3$	8.6	8.6 ± .7	11.3 ± .2	6.6 ± .4	264.6 ± .6	256.0 ± .6	266.9 ± .2	87.5 ± .5
$(CH_3)_2CO$	9.3	——	——	6.7 ± .4	260.6 ± .5	260.6 ± .5	271.2 ± .2	87.6 ± .5
$(CH_3)_2SO$	9.3	——	——	7.0 ± .4	259.3 ± .5	259.3 ± .5	270.7 ± .2	85.5 ± .5
CH_3CN	9.8	——	——	6.8 ± .4	258.4 ± .5	258.4 ± .5	269.6 ± .2	87.6 ± .5
CH_3NO_2	10.3	3.1 ± 1.5	9.3 ± .2	6.5 ± .4	262.1 ± 1.1	258.9 ± 1.1	269.8 ± .2	85.2 ± .5
CH_3I	10.3	6.0 ± .9	11.4 ± .2	7.0 ± .4	261.6 ± .6	255.6 ± .6	265.9 ± .2	83.2 ± .5
Ac_2O	9.9	4.6 ± 1.4	11.3 ± .2	6.6 ± .4	262.8 ± 1.0	258.2 ± 1.0	269.1 ± .2	84.6 ± .5
DMF	10.1	2.5 ± 1.8	10.2 ± .2	6.5 ± .4	263.3 ± 1.1	260.9 ± 1.1	272.1 ± .2	85.2 ± .5
EtOH	12.5	7.4 ± .8	11.4 ± .2	6.5 ± .4	260.5 ± .6	253.1 ± .6	264.4 ± .2	83.4 ± .5
t-BuOH	9.4	5.7 ± 1.0	10.0 ± .2	6.5 ± .4	261.3 ± .7	255.6 ± .7	262.3 ± .2	83.5 ± .5
t-BuOH	4.8	——	——	6.2 ± .4	——	——	——	——
Et_2O	10.6	9.0 ± .7	12.0 ± .2	6.8 ± .4	261.8 ± .5	252.8 ± .5	265.3 ± .2	87.6 ± .5
Dioxane	9.8	6.9 ± .9	11.5 ± .2	6.0 ± .4	263.5 ± .6	256.7 ± .6	267.2 ± .2	85.1 ± .5
Dioxane	5.0	6.9 ± .9	11.5 ± .2	6.0 ± .4	262.9 ± .6	256.0 ± .6	260.9 ± .2	83.4 ± .5
THF	8.1	6.3 ± .9	11.5 ± .2	6.2 ± .4	263.4 ± .6	257.2 ± .6	267.6 ± .2	82.7 ± .5

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PROPOSITIONS

PROPOSITION 1

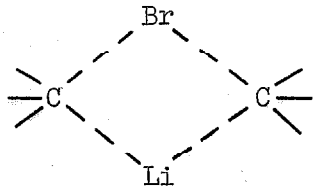
A radical mechanism is proposed for the metal-halogen exchange reaction.

Considering the great synthetic utility of the metal-halogen exchange reaction (1,2), surprisingly little is known about its mechanism.

$$RLi + R'X \rightleftharpoons RX + R'Li$$

The reaction is reversible, and favors an equilibrium product distribution in which the lithium atom is bonded to the least electropositive carbon atom (3). Exchange probably proceeds by front-side attack of the organometallic on the alkyl halide, since the overall stereochemical result of a reaction sequence involving metal-halogen exchange between an optically active halide and an alkyllithium compound, followed by carbonation, has been shown in several instances to be retention (4).

On the basis of these few data, the interchange of the lithium atom and the halogen atom is commonly considered to take place <u>via</u> a concerted four-center transition state:



It is proposed that the metal-halogen exchange reaction may actually occur in two distinct steps, and proceed <u>via</u> a linear transition state. In the first, rate-determining step, the alkyllithium

compound would donate an electron to the halogen atom, forming the corresponding alkyl radical and alkyl halide radical-anion; in the second step, the alkyl radical would displace the halogen atom from the radical anion via a linear transition state or

$$R\text{-}Li + R'Br \longrightarrow R\cdot + R'Br^{\cdot-}\ Li^{+}$$

$$R\cdot + R'Br^{\cdot-}\ Li^{+} \longrightarrow R\text{-}Br^{-}\text{-}R'Li^{+} \longrightarrow RBr + R'Li$$

intermediate containing a halogen atom with an expanded octet. This mechanism is analogous to that proposed by Russell and co-workers for the oxidation of anions (5).

A mechanism for the exchange reaction involving electron transfer in the rate-determining step predicts that the reaction should proceed most rapidly between alkyl halides which have high electron affinities and organolithium compounds which are good electron donors. Unfortunately, only qualitative data are available concerning the electron affinities and ionization potentials of these compounds. Alkyl halides are known to have relatively high electron affinities from studies of their dissociative electron capture in solution (6); data from polarographic studies indicate that the ease of reduction (and presumably the electron affinity) for structurally similar alkyl halides increases in the order Cl < Br < I (7). The ionization potential of only one organolithium compound, ethyllithium hexamer, has been determined with any certainty. The electron impact appearance potential of $(CH_3CH_2)_5Li_6^{+}$ has been found to be 7.7 e.v. (8) (this value may be compared with that for ethane (11.7 e.v.), ethyl radical (8.7 e.v.) and benzene (9.6 e.v.)).

The low value of the ionization potential for ethyllithium hexamer supports the intuitive belief that the strongly basic organolithium reagents should have relatively low ionization potentials. If one assumes that the more basic organolithium reagents will have lower ionization potentials, both of these considerations are consistent with the qualitative experimental observation that the exchange reaction proceeds most readily when the reagents used are alkyl iodides and secondary or tertiary organolithium compounds. Unfortunately, the rate of the concerted mechanism would be predicted to vary in the same fashion with the character of the reagents, on the basis of polarizability and base-strength.

The best method of demonstrating a radical mechanism for this reaction would be direct observation of the postulated radicals by e.p.r. spectroscopy. However, the short life-time and low concentrations of these species would probably make such spectroscopic detection difficult. Alternatively, it is proposed that the halogen-containing products from reaction of 2,2-diphenylpropyllithium with ethyl bromide at 0° be examined. The organolithium compound has been shown not to

$$\phi_2C(CH_3)CH_2Li + CH_3CH_2Br \longrightarrow \phi_2C(CH_3)CH_2\cdot + CH_3CH_2Br^{\cdot-}\ Li^+$$

$$\phi_2C(CH_3)CH_2\cdot \xrightarrow{k_2} \phi\dot{C}(CH_3)CH_2\phi$$

$$\phi_2C(CH_3)CH_2\cdot + CH_3CH_2Br^{\cdot-}\ Li^+ \xrightarrow{k_3} \phi_2C(CH_3)CH_2Br + CH_3CH_2Li$$

$$\phi\dot{C}(CH_3)CH_2\phi + CH_3CH_2Br^{\cdot-}\ Li^+ \xrightarrow{k_3'} \phi CBr(CH_3)CH_2\phi + CH_3CH_2Li$$

rearrange at this temperature (9). The neophyl radical rearranges extensively at 30° (10); 2,2-diphenylpropylradical should therefore rearrange very rapidly, even at 0°.

Observation of 2-bromo-2,3-diphenylpropane among the products would suggest strongly that free alkyl radicals were involved in this reaction. Unfortunately the absence of this compound would not permit an umambiguous decision concerning the mechanism, because it is conceivable that k_2 in the above scheme might be appreciably less than k_3.

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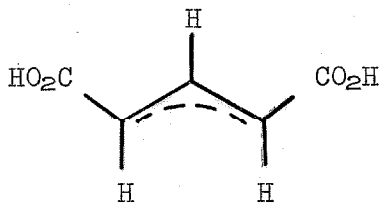
PROPOSITION 2

An experiment to detect radical reactivity at the β position of allyl radical is proposed.

Molecular orbital treatments which take into account electron correlation differ from simpler single-configuration Hückel theory in predicting an appreciable spin density in the p orbital on the central carbon atom of allyl radical (1). This prediction has been confirmed experimentally for the substituted allyl radical I, observed in X-irradiated glutaconic acid (2).

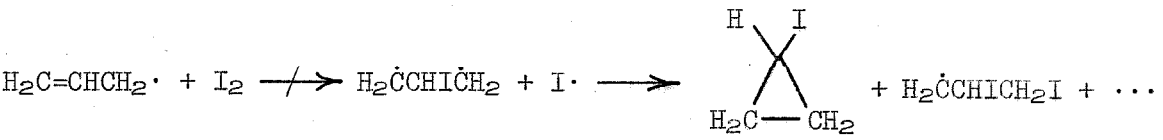


I

Values of the p orbital spin densities ρ at the three central carbon atoms of this molecule have been determined to be $\rho_1 = \rho_3 = 0.57$ and $\rho_2 = -0.19$, by analysis of its e.p.r. spectrum (2).

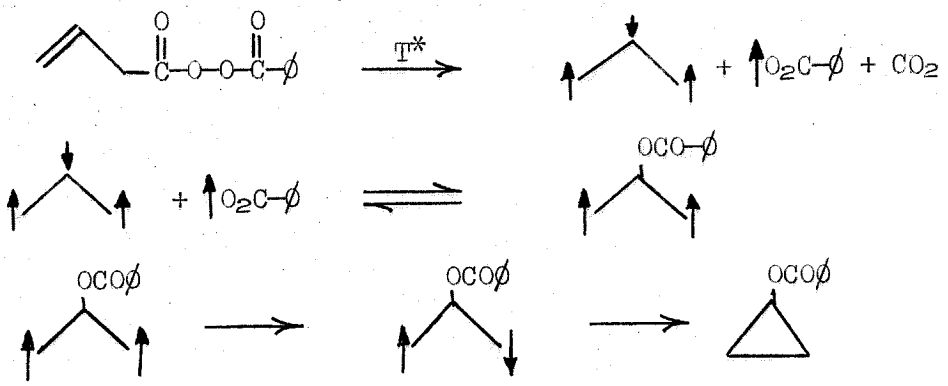
The physical significance of the difference in the sign of ρ_1 (or ρ_3) and ρ_2 is most easily understood if the radical is considered to be in a magnetic field. The unpaired electron of the radical, imagined as a classical magnetic dipole, can be oriented either parallel or antiparallel to this field. The difference in the sign of ρ at C1 and C2 indicates that if the electronic magnetic dipole is aligned parallel to the field at C1, it will appear to be aligned antiparallel at C2, and vice versa.

Although the magnitudes of the spin densities at the α and β carbon atoms of allyl radical suggest that both positions have appreciable radical character, there are no reported examples of reactions suggesting radical reactivity at the β position. This unreactivity at the β position in normal radical reactions is not unexpected, because such reaction (outlined schematically below for reaction with iodine) would involve formation of a high-energy biradical intermediate, and because the higher spin densities at the α



and γ carbon atoms should favor reaction at these centers (3).

It is proposed that the cage products from reaction of allyl radical with benzoyloxy radical, produced by the triplet photosensitized decomposition of propionyl benzoyl peroxide, might demonstrate appreciable reactivity at the β carbon atom of allyl radical. Two factors in this system favor reaction at the β position. First, the proposed reaction is a radical-radical reaction, and attack by the benzoyloxy radical at either the α or β position of the allyl radical should have a relatively low activation energy. Benzoyloxy radical should therefore be less selective in the position of its attack than iodine. Second, if the electron correlation between the two radicals initially formed in the cage is sufficient to maintain their triplet character for a period of time greater than the time required for them to couple, only reaction at the β position of the allyl radical could occur without a change in multiplicity. (In these formulas, the arrow indicate the electron spin at the pertinent positions.)



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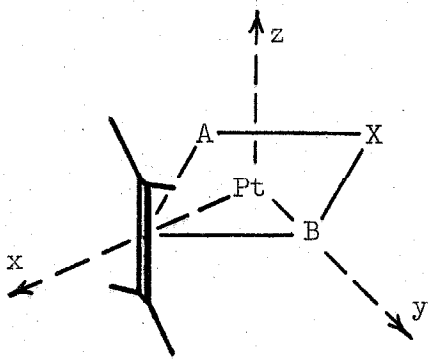
PROPOSITION 3

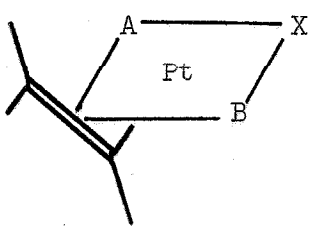
It is proposed that the rate of rotation around the platinum-olefin bond of platinum(II)-olefin complexes will show a trans effect, and that the magnitude of this effect will provide a qualitative measure of the contribution of the metal $6p_z$ orbital to the metal-olefin bond.

The metal-olefin bond of a platinum-olefin complex is commonly considered to consist of two separate although related components (1): a σ-type component resulting from overlap of the filled olefin π orbital with an empty dsp^2 metal orbital, and a π-type component from overlap of a filled dp metal orbital with the empty olefin π^* orbital. The relative contribution of the two components to the metal-olefin bond energy is not known with certainty.

X-ray diffraction studies of Zeise's salt (2) and of the complexes between palladium chloride and ethylene (3) and styrene (4) have demonstrated that the axis of the carbon-carbon olefinic bond normally lies perpendicular to the plane formed by the metal and the three ligands A, B and X (Ia).



Ia



Ib

If the coordinate axes in the complex are defined as indicated by Ia, the metal orbitals whose mixing results in the formation of the $\underline{dsp^2}$ hybrid orbitals will be the $5\underline{d}_{x^2-y^2}$, $6\underline{s}$, $6\underline{p}_x$, and $6\underline{p}_y$ orbitals; the $5\underline{d}_{xy}$ and $6\underline{p}_z$ metal orbitals will form the $\underline{dp}$ hybrid orbitals.

The transition state for rotation around the olefin-metal bond will probably have the geometry indicated by Ib: the two carbon atoms, the metal and the three ligands A, B and X will all lie in a common plane. The σ-component of the olefin-metal bond should not be much altered by the 90° rotation around the bond axis required to take Ia to Ib, because the $\underline{dsp^2}$ orbital will have approximately cylindrical symmetry. The energy of the π-component, however, will decrease by an amount which depends upon the contribution of the $6\underline{p}_z$ orbital to the olefin-metal bond in Ia and Ib. In Ia, the π-component is formed by overlap between a π^* olefin orbital and a $\underline{dp}$ metal hybrid orbital. In Ib, the only orbital available for overlap with the π^* orbital is the $5\underline{d}_{xy}$ orbital, because the $6\underline{p}_y$ orbital (which has the same geometry relative to the olefin π^* orbital in Ib as does the $6\underline{p}_z$ orbital in Ia) is involved in bonding with the A and B ligands. In other words, the energy of the π-component of the metal-olefin bond in Ia depends on overlap between a π^* olefin orbital and a $\underline{dp}$ metal orbital; in Ib it depends on the less effective overlap between the π^* orbital and a $\underline{d}$ metal orbital.

Experimental measurement of the energy difference between Ia and Ib due to the difference in the energy of the metal-olefin π-bond in these two conformations could be accomplished by measuring the activation parameters for rotation around the metal-olefin bond, were

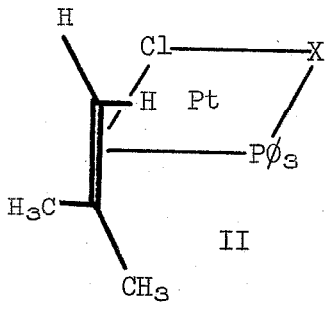
it not for a probably considerable contribution to these parameters from steric interactions between the hydrogens on the olefin and the ligands A and B. Alternatively, it is proposed that determination of the response of the rate of rotation to the character of the trans ligand X will provide a qualitative measure of this energy difference (5).

The ligand X trans to the olefin could exert its influence on the rate of rotation either through its effect on the olefin-metal dative π-bonding, or through its effect on the total olefin-metal bond strength (5). Rotation around the olefin-metal bond should not markedly affect the σ contribution to the metal-olefin bond. The effect of the trans ligand X on this component can therefore be neglected. The π-component of the metal-olefin bond will however be affected by rotation, to the extent that the overlap between the olefin π^* orbital and the metal orbitals is determined by the $6p_z$ orbital.

An electronegative ligand X capable of forming strong acceptor d-d π-bonds with the metal will compete with the olefin π^* orbital for the electrons in the metal d orbitals. The more strongly X polarizes the electron density in these d orbitals away from the olefin, the weaker will be the π-component of the olefin-metal bond, and correspondingly, the smaller the difference between the π contributions to the olefin-metal bonds in Ia and Ib. (This decrease in the contribution of the π bonding to the barrier to rotation on increasing the acceptor strength of X is most simply understood for a hypothetical ligand capable of reducing the energy of the π-component of the olefin-metal bond to zero for both Ia and Ib; clearly in this extreme the π contribution to

the barrier would be zero.) Consequently, the magnitude of the trans effect on the rate of rotation around the metal-olefin bond will be a measure of the difference in the importance of π-bonding in Ia and Ib, and correspondingly a qualitative measure of the contribution of the $6p_z$ orbital to the olefin-metal bonding.

Determination of the necessary rates of rotation might be accomplished by following the rate of racemization of optically active II (if rotation is slow), or by determination of the temperature dependence



II

of the n.m.r. spectrum of racemic II (if rotation is rapid).

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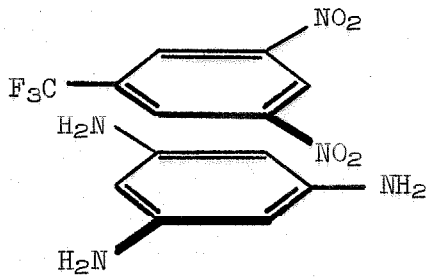
PROPOSITION 4

An intermolecular coupling constant is proposed.

Spin-spin coupling between two protons in a saturated organic compound is commonly agreed to occur through the agency of the electrons in the σ-bonds joining the two (1). However, considerable experimental evidence has accumulated suggesting that coupling involving fluorine (2,3) or heavy nuclei (4) may take place by other mechanisms than the through-bond Fermi contact coupling important for protons. In particular, it has been suggested that fluorine-fluorine (2) and fluorine-hydrogen (3) couplings may reflect interactions between the nuclei occurring through space, rather than through the intermediacy of the σ-bonding electrons.

Experimental attempts to distinguish between through-space and through-bond couplings are made difficult by the fact that changes in the geometry of a molecule designed to bring two nuclei of interest close together or to hold them apart are also expected to change the magnitude of any coupling through the σ-bonds connecting the two (1). Consequently, interpretation of the dependence of a coupling constant on the geometry of a molecule, in terms of the relative contribution of through-bond and through-space contributions, is rather ambiguous. Observation of an intermolecular coupling constant between nuclei on different molecules would demonstrate clearly that two nuclei need not necessarily be connected by σ-bonds in order to be coupled. It is proposed that an intermolecular coupling constant might be observed at low temperature in a charge-transfer complex of the type exemplified by 1:



I

Two practical problems must be considered in proposing that the fluorine atoms in this complex will show appreciable spin-spin coupling to the ring hydrogens on the triaminobenzene ring. The first is the lifetime of the complex in solution; the second is the proximity of the fluorine atoms to the protons in the second ring.

If the rate of exchange between complexed and uncomplexed molecules is greater than the intermolecular fluorine-hydrogen coupling constant, the coupling will have no effect on the spectrum (5).

The rate of this exchange is difficult to predict accurately. Formation of charge-transfer complexes is known to be too rapid for measurement by ordinary kinetic techniques (6). Consequently the activation energy for formation of a complex must be small, and the energy required to dissociate a complex should be approximately equal to its heat of formation. For moderately strong complexes (for example, the complex of anthracene with s-trinitrobenzene) measured heats of formation are approximately 4 kcal./mole (7). If the activation energy for exchange is assumed to be approximately equal to the energy required to

dissociate the complex, it seems possible that a strong complex might have a dissociation energy of 6-8 kcal./mole, and consequently an exchange rate sufficiently slow to be observable at low temperatures by n.m.r. spectroscopy.

The second problem to be considered is that of the distance in the complex between the potentially coupled nuclei: unless the hydrogen-fluorine distance is small, there seems little hope of observing through-space coupling. Crystal structure determinations of several aromatic charge-transfer complexes indicate that the planes containing the donor and acceptor molecules are separated by 3.2-3.5 Å (8). Assuming that the van der Waals radius of a trifluoromethyl group is approximately 2.1 Å (the radius of a hydrogen atom is 1.2 Å; of a fluorine atom, 1.35 Å; and of a methyl group 2.0 Å)(9), the minimum distance between the fluorine atoms of one ring and the hydrogen atoms of the second is approximately equal to the sum of their van der Waals radii. Petrakis and Sederholm have suggested that van der Waals contact may be a necessary condition for through-space coupling (2).

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PROPOSITION 5

An experiment is proposed to clarify certain details of the mechanism of the formation of alkylcobalt tetracarbonyls from acylcobalt tetracarbonyls.

The facile reaction of an alkylcobalt carbonyl compound with carbon monoxide to yield the corresponding acylcobalt carbonyl forms the basis for a variety of industrially important carbonylation reactions (1). The experimental foundation of most discussions of the mechanism of this transformation has been a study by Coffield, Kozikowski and Closson of the analogous alkyl-acyl interconversion in methylmanganese pentacarbonyl (2). Using ^{14}C labeled carbon monoxide, these workers demonstrated that the carbon monoxide molecule which was incorporated into the acetyl group was not that which entered the complex from solution, and conversely that during decarbonylation the carbon monoxide fragment from the acetyl group remained attached to the metal and did not escape directly into solution.

$$CH_3Mn(CO)_5 + {}^{14}CO \longrightarrow CH_3\overset{O}{\overset{\|}{C}}Mn(CO)_4({}^{14}CO)$$

$$CH_3{}^{14}\overset{O}{\overset{\|}{C}}Mn(CO)_5 \longrightarrow CH_3Mn(CO)_4({}^{14}CO) + CO$$

The reasonable assumption is commonly made that an analogous result would be observed for the alkylcobalt tetracarbonyl- acylcobalt tetracarbonyl interconversion, and that the acyl carbonyl group would remain tightly bound to the metal atom during these reactions. The question of the degree of freedom to be ascribed to the alkyl group

in this interconversion is presently unanswered. Calderazzo and Cotton have suggested that migration of the alkyl group from carbon monoxide molecule to metal and back occurs within the confines of the complex (4). A reaction of this type would have ample precedent in the condensation reactions observed for acetylenes and carbon monoxide bound as ligands to low-valence transition metal ions (5). However the reaction might also proceed by the more mundane free radical pathway outlined schematically below:

$$RCo(CO)_4 \rightleftharpoons R\cdot + Co(CO)_4$$

$$R\cdot + Co(CO)_4 \rightleftharpoons RCOCo(CO)_3$$

$$RCOCo(CO)_3 + CO \rightleftharpoons RCOCo(CO)_4$$

(This reaction scheme has been written in terms of coordinately unsaturated intermediates, following a suggestion of Heck (6); alternatively, unstable intermediates of the type

$$R\cdot + Co(CO)_5$$

might be invoked.)

Carbonylation proceeding through an alkyl free radical intermediate would require that radical addition to the carbon monoxide molecules in the coordination sphere of the metal be rapid. Although radical additions to carbon monoxide have not been examined in any detail, both the ability of ethylene to copolymerize with carbon monoxide (7) and the calculated low activation energy for radical addition to this molecule (8) suggest that such addition might be facile.

In order to distinguish between a mechanism for the carbonylation reactions involving free and tightly bound alkyl groups, it is proposed that optically active 2-methylbutyrylcobalt tetracarbonyl (9) be decarbonylated and the extent of racemization of the resulting isobutylcobalt tetracarbonyl be determined. A high degree of stereospecificity in the reaction would exclude a mechanism involving appreciable freedom in the alkyl group. Before extensive racemization could be taken as evidence for a free alkyl group, it would be necessary to establish the optical stability of optically active isobutylcobalt tetracarbonyl (10), under the reaction conditions. However the high degree of covalency expected for the carbon-cobalt bond (11) suggests that the asymmetric center of this organometallic compound should be configurationally stable.

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